Anais XIII Simpósio Internacional de HTLV no Brasil

Journals BAHIANA
SCHOOL OF MEDICINE AND PUBLIC HEALTH

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Ficha Catalográfica elaborada pelo Sistema Integrado de Bibliotecas

S216a Simpósio Internacional de HTLV no Brasil (13.: 2017: Salvador, BA).
Anais [recurso eletrônico] / XIII Simpósio Internacional de HTLV no Brasil, 11 a 13 de setembro de 2017. / Centro de Convenções da BAHIANA. Salvador, Bahia, Brasil.

Disponível em: www.journals.bahiana.edu.br

Inclui referências

1.HTLV no Brasil. 2. Infecção. 3. Epidemiologia. 4. Simpósio. I. Abrahão Neto, José, org. II. Bastos, Maria de Lourdes, org. III. Braga, Silvane, org. IV. Gadelha, Sandra, org. V. Goes, Eugenia Pontes de, org. VI. Gois, Luana Leandro, org. VII. Hialla, Thessika, org. VIII. Jesus, Adijeane Oliveira de, org. IX. Mascarenhas, Rita Elizabeth Moreira, org. X. Santos, Claudio Paulo dos, org. XI. Silva, Carlos Gustavo Regis da, org. XII. Título. XII. Anais do XIII Simpósio Internacional de HTLV, no Brasil.

CDU:
616.1

APOIO E REALIZAÇÃO

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XIII SIMPÓSIO INTERNACIONAL DE HTLV NO BRASIL

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XIII INTERNATIONAL SYMPOSIUM ON HTLV-1 IN BRAZIL SALVADOR-BAHIA 2017

The XIII International Symposium on HTLV-1 took place from September 11 to 13, 2017, in the city of Salvador, Bahia, under the coordination of Dr. Maria Fernanda Rios Grassi and Dr. Bernardo Galvão-Castro. The event featured numerous lectures, roundtable discussions and sharing of scientific knowledge regarding the current situation, as well as advances in HTLV research in Brazil. The symposium was attended by renowned researchers from several Brazilian Institutions who presented their experiences in the areas of research and clinical care. The covered topics included epidemiology, nursing, clinical and psychological manifestations, laboratory diagnosis, family aggregation, treatment, new biomarkers and future perspectives in the country. One of the symposium's highlights was the elaboration and distribution of a patient manual, produced by physiotherapists from the Bahian School of Medicine and Public Health, containing guidelines and exercises for individuals with HAM/TSP. The event's target audience included researchers, physicians, practitioners and health sciences students. Patients were also invited to actively participate, some of whom shared health care concerns. Representatives from associations whose members consist of individuals living with HTLV (Associação HTLVida and Grupo Vitamore) were also in attendance. In addition, two renowned Brazilian researchers were honored for their contributions in the field of HTLV research: Dr. Achiléa Bittencourt and Dr. Fernando Proietti.

Due to the neglected status of HTLV-1 infection and associated diseases in Brazil, the "Brazilian Society of Human and Animal Retrovirology" was founded during the symposium. This society aims to promote HTLV research and associated diseases, stimulate research collaborations, aid in the dissemination of knowledge regarding the infection, and strengthen public health policies. The Brazilian Society of Human and Animal Retrovirology plans to closely collaborate with the International Association of Retrovirology (http://www.htlv.net/).

EDIÇÕES DO SIMPÓSIO INTERNACIONAL SOBRE HTLV NO BRASIL – LOCAIS, DATAS E PRESIDENTES

I Simpósio Internacional sobre HTLV no Brasil
São Paulo, 1992
Dr. Nelson Hamerschlak

II Simpósio Internacional sobre HTLV no Brasil
Rio de Janeiro, 1993
Dra. Maria do Socorro Pombo

III Simpósio Internacional sobre HTLV no Brasil
Recife, 1994
Dra. Paula Loreiro

IV Simpósio Internacional sobre HTLV no Brasil
Belo Horizonte, 1996
Dra. Anna Barbara Proietti

V Simpósio Internacional sobre HTLV no Brasil
Ceará, 1998
Dr. Carlos Maurício Castro Costa

VI Simpósio Internacional sobre HTLV no Brasil
Salvador, 2000
Dr. Bernardo Galvão Castro Filho.

VII Simpósio Internacional sobre HTLV no Brasil
Belém, 2002
Dr. Ricardo Ishak

VIII Simpósio Internacional sobre HTLV no Brasil
São Paulo, 2005
Dr. Aluísio Segurado

IX Simpósio Internacional sobre HTLV no Brasil
Belo Horizonte, 2006
Dra Anna Bárbara Carneiro-Proietti

X Simpósio Internacional sobre HTLV no Brasil
Rio de Janeiro, 2008
Dr. Abelardo de Queiroz Campos Araújo.

XI Simpósio Internacional sobre HTLV no Brasil
Olinda, 2011
Dra. Paula Loreiro

XII Simpósio Internacional sobre HTLV no Brasil / IV Simpósio Paulista de HTLV
São Paulo, 2014.
Dr. Jorge Casseb

XIII Simpósio Internacional sobre HTLV no Brasil / I Encontro de HTLV da Bahia
Salvador, 2017
Dra. Maria Fernanda Rios Grassi

INSTRUCTIONS TO AUTHORS FOR THE PREPARATION OF ABSTRACTS

- All abstracts must be written in English and formatted using this document as a template.
- Each abstract should be no more than 400 words.
- Abstracts MUST describe the following: Background; Methods; Results; Conclusion
- The margins should be 30 mm at the top, 25 mm at the bottom and 25 mm on the left and right sides.
- Only the Times New Roman and Symbol fonts are permitted. Times New Roman italics can be used for variables.
- The title of the abstract should be written in Times New Roman, bold, 14 pt, centered. Initial letters of each word should be capitalized.
- Authors' names and affiliations should be written in Times New Roman, 12 pt, centered. Initial letters of each word must be capitalized. If there is more than one affiliation, superscript numbers should be used to designate the authors that correspond to each affiliated institution.
- Abstract text should be written in Times New Roman, Times New Roman italics, or Symbol, 12 pt, justified.
- No figures or tables are permitted.
- Use only SI units.
- Formulas and special characters can be used, but special care should be taken that these do not change the line spacing from the 12 pt spacing.
- If your abstract describes a clinical trial, please also write the registration number below.
- Save your abstract in Microsoft Word format and then upload it using the online abstract submission form.
- Categories accepted: Animal model; Molecular & cellular biology; Clinical research (ATL); Clinical research (HAM and inflammatory disease); Epidemiology; Immunology; Virology; Infection control & laboratory tests.

CARLOS MAURÍCIO DE CASTRO COSTA AWARD
RULES FOR THE EXPANDED ABSTRACT

- The abstract can be written in Portuguese or in English, using Arial size 12 and spacing of 1,5
- The main text should include:

01. Identification (in a separate sheet)
(i) Title
(ii) Name(s) of the author(s); in case of more than one author, please indicate who will compete for the award, placing he/she as the first author
(iii) Afilliation of the author(s)

02. Contents
(i) Introduction – maximum of one page; there is no need for subdivisions and it should include:
- a brief presentation of the problem
- a brief review of the state of the art of the problem
- the importance of the project
- the objective(s)

(ii) Materials and Methods – maximum of two pages
- population and/or laboratory samples (indicating the selection method and ethical considerations)
- description of methods in agreement with the objectives

(iii) Results – maximum of two pages for the text; maximum of two Tables and two Figures; Tables and Figures should be placed in separate sheets

(iv) Discussion – maximum of two pages

(iii) References – maximum of twenty references, which should be placed in alphabetical order and numbered; the references should be placed in the main text as numbers only

- All the material should be sent as a single document to the e-mail of the Symposium: simposiohtlv@gmail.com
- Deadline for receipt is 11:59 pm of 21 August 2017 (Brasilia local time)
- It is mandatory that all the Abstracts should be registered for presentation during the Symposium, as well as the first author

SUMÁRIO

VIROLOGY

EXTENDED ABSTRACTS

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P-1

VAGINAL LUBRICATION IN HTLV-1-INFECTED WOMEN

Adenilda Lima Lopes Martins[1;2], Alisson de Aquino Firmino[2], Jean Paulo Lacerda Araujo[2], Taiane Silva Paixao[2], Ney Boa Sorte[2], Maria Fernanda Rios Grassi[2,3], Bernardo Galvão Castro Filho[2,3]

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Background: Human T-lymphotropic virus type 1 (HTLV-1) infection is associated with xerosis, xerostomia (dry mouth) and xerophthalmia, indicating an occurrence of dry syndrome. This study aims test the hypothesis that infection with HTLV-1 is associated with dry vagina. **Methods.** This is a cross-sectional study. Women infected with HTLV-1 and not infected (comparison group), accompanied in a specialized health service in Salvador, Bahia, were sequentially included. Inclusion criteria were: age between 20 and 50 years old and sexual activity in the last 4 weeks. Menopausal women were excluded. All volunteers answered the questionnaire Female Sexual Function Index (FSFI) and underwent to a gynecological consultation to assess vaginal mucosa dryness. The value of maturation (VM) was based on hormonal maturation index. The humidification of the mucosa was measured using a Schirmer's test strips in contact with vaginal membrane for 3 minutes. Dry vagina diagnosis was considered if: FSFI Lubrication Scores< 3, Schirmmer tape values ≤ 5mms and VM <50%. **Results.** 112 women were evaluated (63 HTLV-1-infected and 49 HTLV-1 non-infected). The average age was 34.7 ± 7.0 years in HTLV-1 group and 35.6 ± 7.9 years in the control group (p = 0.53%); 78.8% of women were married or in a stable union in the HTLV-1 group and 71.4% in the control group. The median found in the vaginal lubrication domain FSFI was 4.8 (IIQ 3.6-5.4) in the HTLV-1 group, similar to that of control group 4.8 (IIQ 4.2-5.7), p = 0.31. Lubrication scores in FSFI <3 were found in 13.7% of HTLV-1 infected, compared to 10.2% in the negative controls. The mean Schirmer test value in the vaginal mucosa was 13.1 ± 4.7 mm in HTLV-1 infected women and 13.2 ± 5.0 mm in the control group, p = 0.253.) Schirmer strip ≤ 5 mm was found at 7.9% of HTLV-1 and 4.1% of the controls. The average of the VM was 72.2 ± 4.7% for women infected with HTLV-1 and 74.8 ± 12.4% to the uninfected, p = 0.337. VM < 50% has been found in 1.6% of HTLV-1 infected women and 2.0% of the controls. **Conclusion.** HTLV-1 infection was not associated with the presence of dryness of the vaginal mucosa in asymptomatic women. Further studies involving women with diseases associated with infection by HTLV-1 are needed.

Key words: HTLV-1, Female Sexual Function Index, Dry vagina, vaginal lubrication, value of maturation.

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P-2

PROPOSAL OF PHYSICAL REHABILITATION FOR HTLV-1-ASSOCIATED MYELOPATHY (HAM/TSP) PATIENTS

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Background: The HTLV-1 infects approximately 15-20 million individuals worldwide. Although most infected individuals remain as asymptomatic carriers throughout life, approximately 2-5% develop a progressive and disabling neurological disease called HAM/TSP (Osame, 1990). As the disease progresses, the muscular weakness and the elastic hypertonia generate abnormal patterns of lower limbs movements, reducing walking capacity and the performance of daily activities. To date, there is no specific treatment for the infection. Given this, the early physical therapy becomes essential to manage functional changes and increase the autonomy of these patients. We propose a treatment protocol for patients with HAM/TSP based on the functional disability rating. **Methods:** Literature review using HAM/TSP and functional disability keywords. The consultation was based on electronic databases such as Medline, Pubmed, and Lilacs, in articles in Portuguese, English and Spanish. **Results:** In addition to the muscular weakness observed with predominance in the knee and dorsiflexor, several groups present elastic hypertonia with consequent secondary alterations, such as muscle shortening. The hip adductor and plantiflexor muscles are the most affected by spasticity, directly interfering with walking ability (Caiafa et al, 2016). Physiotherapeutic Rehabilitation Proposal: 1. Strengthening of the paretic muscle through repeated muscular exercise to reduce spasticity, improve neuromuscular control and tissue extensibility; 2. Stretching and better biomechanical alignment of these muscle groups through joint mobilization techniques, passive and sustained stretching, associated with passive exercises and free assets for the maintenance of osteomioarticular integrity; 3. Exercises using elastic bands, shin guards, manual resistance of the therapist or with the action of gravity focusing on the muscles involved in the gait cycle (extensors, flexors and hip abductors, knee flexors and dorsiflexors); 4. Training should include concentric, eccentric and isometric activities, prioritizing exercises in closed kinetic chain under different situations and contexts, simulating functional activities; 5. Specific maneuvers of the Proprioceptive Neuromuscular Facilitation (FNP) technique applied to the pelvic girdle, trunk and lower limbs contribute effectively to the facilitation of gait patterns; 6. Aerobic conditioning exercises (exercise bicycle, treadmill or cycloergometer upper limbs) can be used as adjuvants thus optimizing cardiorespiratory capacity and minimizing the fatigue of these patients. **Conclusion:** Due to the chronic and progressive character of HAM/TSP, the inevitable disability picture highlights the importance of a physiotherapeutic protocol aimed on the affected muscle groups, promoting the improvement of the status functional and consequent improvement of the quality of life.

Key words: HTLV-1; rehabilitation; HAM/TSP

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P-3

LEVELS OF PROINFLAMMATORY CYTOKINES AND CLINICAL WORSENING IN PATIENTS DIAGNOSED WITH HTLV-1

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Background: HTLV-1-Associated myelopathy/Tropical Spastic Paraparesia (HAM/TSP) is a neurological disorder developed by approximately 0.25–3.8% of patients with human T-Lymphotropic Virus type 1 (HTLV-1). The main symptoms are the progressive impairment of gait and sphincter control. The reducing regulation of pro and anti-inflammatory cytokines alters the immune response and promotes the emergence of symptoms. However, there are few studies that address the influence of inflammatory mediators on the clinical evolution of these patients. The aim of this study was to investigate the relationship of cytokines (IL-2, IFN-γ, TNF-α, IL-4, IL-6 and IL-10) with spasticity, muscle weakness in the lower limbs, urinary symptoms, and gait quality in HTLV-1 patients at the Palliative Care Unit of the Oswaldo Cruz University Hospital (HUOC). **Methods:** Twenty-seven patients, of both sexes (74.1% female and 25.9% male) with mean age of 49.2 ± 12.3 years were evaluated. Clinical data were obtained by questionnaire and motor assessment was performed by the Spastic Paraplegia Rating Scale (SRPS). The cytokines IL-2, IFN-γ, TNF-α, IL-4, IL-6 and IL-10 were measured from the serum of patients, using Cytometric Bead Array (CBA). IL-6 levels were significantly higher in patients with worse gait quality ($p = 0.02$) and also in patients with spasticity in hamstrings muscles ($p = 0.03$). An elevation of TNF-α levels was associated with a presence of urinary symptoms ($p = 0.03$). There was no association between cytokines IL-2, IFN-γ, IL-6 and IL-10 with clinical parameters. **Results:** The results of this study point out that the imbalance of inflammatory response, by increase of proinflammatory cytokines levels, is associated with clinical worsening of HTLV-1 patients. It also reinforces the need to perform specific laboratory tests, as well as the importance of functional evaluation in monitoring the clinical evolution of these individuals.

Key words: HTLV-1, proinflammatory cytokines, Spastic Paraplegia Rating Scale, clinical evolution

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P-4

ASSOCIATION OF POLYMORPHISMS IN THE PROMOTER REGION AND ÉXON 1 OF MBL2 GENE AND MENOPAUSE WITH FUNCTION DISABILITY, PAIN AND OCCURRENCE OF HAM/TSP IN WOMEN WITH HTLV

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Background: Human T-cell lymphotropic virus (HTLV) causes HTLV-1-associated Tropical Spastic Paraparesis / Myelopathy (HAM / TSP) in 2-4% of those infected, being more frequent in women ≥ 40 years. The efficiency of the immune response may be influenced by sex hormones and polymorphisms of the mannose-binding lectin gene (MBL2). From the functional point of view, HTLV-1 infection and the development of HAM / TSP affects gait and urinary control, compromising functional capacity and progressively limiting the autonomy and independence of the patients with myelopathy. Thus, the aim of this study was to verify the association of menopause and MBL2 gene with HAM / TSP, functionality and pain. **Methods:** A total of 77 women aged ≥ 40 years with HTLV-1 from HUOC-PE were evaluated. The genotyping of MBL2 was performed using the real-time PCR technique using the Syber Green system with analysis of the melting curve for exon 1 (alleles A or O) and TaqMan system for regions -550 (H / L alleles) and -221 (X / Y). In order to establish the diagnosis of menopause, the concentration of follicle stimulating hormone (FSH) in the blood was measured by Chemiluminescence (Architect i2000 abbott), defined as criteria the FSH concentration above 40 mIU / ml and amenorrhea for a period of more than one year. Functionality was assessed by the functional independence measure and pain was evaluated by visual analogue scale and the McGill pain questionnaire. **Results:** It was observed that the presence of HAM / TSP was significantly associated with menopause ($p = 0.03$), functional dependency ($p < 0.0001$) and polymorphism associated with low MBL production ($p = 0.045$). The LY haplotype (low MBL production) was more frequent in functionally dependent women ($p = 0.006$), indicating functional impairment. On the other hand, the haplotype HY (high MBL production) was more frequent in functionally independent women ($p = 0.045$), indicating protection for the occurrence of HAM / TSP. Pain of neuropathic type ($p = 0.009$) and higher intensity ($p = 0.038$) were more frequent in women between 40 and 60 years. However, polymorphisms were not associated with pain because of the high frequency of this symptom (96.1%), which interfered in the analysis. **Conclusion:** Therefore, women ≥ 40 years in menopause with low MBL production determined genetically are susceptible to HAM / TSP and to functional déficit.

Key words: MBL2 gene, menopause, function disability, HAM/TSP, HTLV

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TUBERCULOSIS INFLUENCE IN HTLV-1 NEUROLOGICAL MANIFESTATIONS

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Background: Human lymphotropic virus type 1 (HTLV-1) infection increases the risk for tuberculosis (TB). This co-infection increases the risks for development of HTLV-1 associated myelopathy or tropical spastic paraparesis (HAM/TSP). However, no previous study has evaluated if TB influences the appearance and the severity of HAM/TSP. The aim of this study was determine if HTLV-1 and TB coinfection predisposes to a greater severity of myelopathy and predisposes the appearance of HAM/TSP. **Methods:** Patients (38) were classified as having TB (history of TB confirmed by the presence of acid-fast bacilli in bacilloscopy), latent TB (absence of clinical history of TB and positive tuberculin skin test [TST]) and without TB (absence of TB and negative TST). Severity of the myelopathy was determined using the Osame scale for motor dysfunction (ODMS) and expanded disability scale score (EDSS). Patients were evaluated in three different periods. At the diagnosis of HAM/TSP, in an intermediate period, and the current (final) evaluation. The Wilcoxon test and the Mann-Whitney test were used to perform statistical analysis. In 7 patients with a past history of tuberculosis we determine if TB influenced the onset of myelopathy evaluating the neurological and urological symptoms presented before and after the diagnosis of tuberculosis. **Results:** The ODMS scale presented the same final severity in the groups with TB, latent TB and without TB. The EDSS scale increased between the initial and final evaluation in the group with TB (from 3 to 6) and decreased in the group without TB (from 6 to 4). However the comparison between these groups was not significant, $p = 0.14$. The diagnosis of tuberculosis preceded that of HAM/TSP in all patients, $p = 0.01$. In 71,4% of these patients neurological and urological symptoms were detected only after the diagnosis of TB ($p = 0.05$). **Conclusion:** Tuberculosis precedes the appearance of HAM/TSP in all patients but TB was not associated with the severity of HAM/TSP.

Key words: HTLV-1, tuberculosis, HAM/TSP.

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P-6

FUNCTIONAL MOBILITY OF PEOPLE WITH AND WITHOUT HAM / TSP: A CROSS-CURRENT STUDY

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Introduction: People infected with Human T-Cell Lymphotropic Virus Type 1 (HTLV-I) may present with HTLV Associated Myelopathy or Tropical Spastic Paraparesis (HAM / TSP), which courses with motor changes and affects functional mobility. **Objective:** To compare a functional mobility of individuals with and without HAM/TSP. **Methods:** A cross-sectional study was carried out with people with and without HAM / TSP referred from a reference center for HTLV care and research, being able to walk with or without gait.Sociodemographic and clinical data were collected. The evaluation of functional mobility was performed using Timed up and Go (TUG). A group between the groups was carried out by means of the student test, considering an alpha of 5%. The project was approved by the CEP of UCSal under CAAE 1.310.107. **Results:** Functional mobility was reduced (in the HAM / TSP group being P.0.001), suggesting an increased risk of falls for these people.Conclusion: People with HAM / TSP have reduced functional mobility which may suggest a greater risk of falls than has been observed in other vulnerable populations.

Key-Words: Mobility Functional. Gait.Human T-lymphotropicvírus 1. Timed Up and Go.

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DIFFERENTIAL TRANSMISSION AND MORBID DIVERSITY ARE PECULIAR FEATURES OF HTLV-1 INFECTION?

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Background: Human T-lymphotropic virus type 1 (HTLV-1) inhabits T-lymphocytes and is transmitted mainly by the transfer of these infected lymphocytes from mother to child, in breastfeeding, and from man to woman by semen, being causal agent of an incapacitating myelopathy (HAM/TSP), adult T-cell leukemia / lymphoma (ATLL), some immune system disorders and other diseases. The high endemicity of HTLV-1 in households in the metropolitan area of Belem city, in Brazil, motivated this study in order to characterize the peculiarities of the transmission and the clinical diversity resulting from the infection. **Methods:** Between 2007 and 2015 were investigated 140 family groups of the confirmed virus carriers (index cases) including 347 communicating members who underwent anti-HTLV-1/2 serological testing by the Elisa method and detection test of proviral DNA in the blood. Clinical aspects were evaluated in all individuals of the families. **Results:** Of the 487 investigated, 63.7% were female, and their frequency was twice as high as men among those infected. The mean age of sample was 41 years, being significantly higher (46 years) in those infected (p> 0.0001). HTLV-1 transmission occurred in 73 families (51.8%) with a concentration of three to four infected / family, prevailing sexual route than the vertical (p = 0.0018). Symptomatic accounted for 44.3% of index cases (62/140) and 9.9% of contacts (11/111). The most prevalent diagnostic modalities were neurological (21.4%) and dermatological (19.3%), with osteoneuromuscular, dysautonomic, xerosis and desquamative skin changes predominating symptoms. The main diseases caused by HTLV-1 among those infected were HAM/TSP (7.2%), Lymphoproliferative diseases (2.6%); Hyperinfestation by S. stercoralis (1.6%); Infective dermatitis (1,2%) and uveitis (0.4%). Parenteral route was the most common form of HTLV-1 transmission in HAM / TSP cases and the vertical pathway in lymphoproliferative diseases including ATL. **Conclusion:** In some of the families, the virus has become embedded by generations of a “sui generis” form, mimicking a genetic factor and suggesting a differentiated behavior in relation to other pathogens. Unequivocal versatility of HTLV-1 has also been observed causing a variety of different clinical conditions in human organisms, many of them configuring well-defined diseases as to the causality of the virus.

Key words: HTLV, infection, transmission, causality, diseases, clinical.

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RISK FACTORS FOR ATHEROSCLEROSIS IN HTLV-1 INFECTED PATIENTS WITH ERECTILE DYSFUNCTION

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Background: Erectile dysfunction (ED) occurs in more than 50% of HTLV-1 infected subjects and in the general population atherosclerosis is the main risk factor associated with ED. There is a direct correlation between severity of ED and the degree of neurologic involvement but ED and severe ED have also been observed in HTLV-1 infected subjects without probable or definitive HTLV-1 associated myelopathy or tropical spastic paraparesis (HAM/TSP). **Objctive:** To compare the contribution of neurologic impairment due to the viral infection versus atherosclerosis as risk factors for ED in HTLV-1 infected individuals. **Methods:** Cross-sectional study with males infected with HTLV-1, age ranging between 18 and 70 years old, classified into two groups according to the presence (cases) or absence of ED (controls). They were compared in regards to obesity, waist circumference, dyslipidemia, metabolic syndrome, diabetes mellitus (DM), high blood pressure (HBP) and neurologic disease. Cases were classified in HTLV-1 carriers (HC) and patients with neurologic disease (probable and definitive HAM/TSP). **Results:** Of the 84 participants, 43 (51.2%) had ED. There was a relationship between ED with age over 60 years (P = 0.002), diabetes mellitus (P = 0.03) and the degree of neurological dysfunction (P <0.001). The odds of ED was highest in patients with neurologic diseases (OR 22.1; 95% CI 5.3-92.3), followed by HBP (OR 6.3; 95% CI 1.4-30.5) and age over 60 years (OR 4.6; 95% CI 1.3-17.3). In males infected with HTLV-1 neurological dysfunction is more associated with ED than risk factors for atherosclerosis. Moreover, in 18HC with ED only 9 had atherosclerosis as risk factors suggesting that involvement of the lumbar and sacral medulla may be the cause of ED in these cases. **Conclusion:** Neurological impairment is the major cause of ED in individuals infected with HTLV-1 and risk factors for atherosclerosis did not have strong relationship with ED in this population.

Key words: HTLV-1; Atherosclerosis; Erectile dysfunction.

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PROPOSAL OF AN ALGORITHM FOR THE DIAGNOSIS OF DRY EYE DISEASE IN INDIVIDUALS INFECTED WITH HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1

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Background: Dry eye disease is an ocular surface disease that causes eye discomfort, visual disturbance, and tear film instability. Infection by Human T-cell Lymphotropic Virus type 1 is associated with dry eye disease. This study evaluated the accuracy of tear film tests and proposed an algorithm for the diagnosis of dry eye disease in those infected with human T-cell lymphotropic virus type 1. **Methods:** Ninety-six patients infected with Human T-cell Lymphotropic Virus type 1 were enrolled in the study. To assess clinical complaints they completed the Ocular Surface Disease Index questionnaire. In order to evaluate the quality of lacrimal film, patients were submitted to tear breakup time test, Schirmer I test and Rose Bengal staining. Dry eye disease was diagnosed when at least two of these three tests were abnormal. Sensitivity, specificity, positive and negative predictive value and overall accuracies of questionnaire and of each test alone and combined in parallel and in series were determined. **Results:** The most sensitive test was tear breakup time test (98%) and the most specific was Schirmer I test (100%). The highest overall accuracy was found for Rose Bengal staining (88.64%) while symptoms assessed using Ocular Surface Disease Index had the lowest overall accuracy (62.65%). Tear breakup time test, Schirmer I test and Ocular Surface Disease Index combined in parallel showed an increase in sensitivity and a decrease in specificity of all tests. Instead, combined in series, tear breakup time test, Schirmer I test and Ocular Surface Disease Index had an increased specificity and decreased sensitivity. **Conclusion:** This study confirmed the need to use more than one test to evaluate the quality of tear film as well as the need to use a symptom questionnaire as part of diagnosis algorithm for dry eye disease.

Key words: HTLV-1; algorithm; dry eye disease

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CLINIC AND IMMUNOLOGIC STUDIES IN HTLV-1 CARRIERS WITH HIGH PROVIRAL LOAD

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Background: High proviral load is the most important risk factor for the human T cell lymphotropic virus type 1 (HTLV-1) associated myelopathy or tropical spastic paraparesis (HAM/TSP), and high levels of proinflammatory cytokines are documented in these patients. However, there are HTLV-1 carriers with a proviral load as high as that documented in patients with HAM/TSP. Moreover an exaggerated inflammatory response is observed in a large proportion of HTLV-1 infected subjects who do not fulfill the criteria for HAM/TSP. In the present study we compare the clinical manifestations and immune response in HTLV-1 carriers (HC) with high and low proviral load. **Methods:** This was a retrospective cohort study with 39 HC being 20 of them (cases) with high proviral load (more than 50.000 HTLV-1 copies / 106 mononuclear cells). These patients were matched by sex and age (±5 years) with 19 HC (controls) with low proviral load (less than 50.000 copies). The individuals answered a questionnaire, physical examination was performed and the neurological status was assessed using neurological scales. Cytokine levels were determined by ELISA and real time PCR was used for evaluation of the proviral load. **Results:** There was no difference between the groups with high and low proviral load regarding age, sex and epidemiologic profile. There was no relevant clinic difference between the groups regarding the presence of urologic, rheumatologic, and neurologic manifestations. The TNF levels (median 386pg/mL [interquartile range 115-1081]) were higher (P<0,05) in cases than in controls (median 53pg/mL [interquartile range 0-491]) at entrance in the study. Moreover, there was a fall in the levels of TNF (p=0,01) and proviral load (p=0,01) after a median of 12 years of follow up only in those who had high proviral load. **Conclusions:** Despite the presence of high proviral load and high cytokine production, it is possible for individuals infected with HTLV-1 to remain in a carrier state. This may occur due to the ability of these subjects to better control HTLV-1 infection, preventing the migration of HTLV-1 infected cells to the central nervous system.

Key words: HTLV-1; HAM/TSP; high proviral load

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ASSESSMENT OF FUNCTIONAL NEUROLOGICAL DISABILITIES IN INDIVIDUALS WITH HTLV-1 ACCORDING TO DEGREE OF NEUROLOGICAL INVOLVEMENT

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Background: Infection with human T-lymphotropic virus 1 (HTLV-1) is a condition associated with Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (TSP/HAM), a progressive and highly debilitating neurological disease. A set of functional assessment measures is used to evaluate the degree of impairment and the functional status of patients with TSP/HAM. To evaluate functional neurological disorders in patients with HTLV-1, using the Expanded Disability Status Scale (EDSS) and Osame Motor Disability Score (OMDS). **Methods:** In the period between March and June 2017, a cross-sectional study was conducted with 39 patients patients who attended the outpatient clinic of the Tropical Medicine Center of the Federal University of Pará, Brazil. All patients had HTLV antibody presence and showed HTLV-1 proviral DNA amplified produtct by PCR. Patients were divided into three groups in descending order of neurological involvement, according to the updated proposal proposal for diagnostic criteria to TSP/HAM: Definitive (Group 1=13); Probable (Group 2=10); Possible (Group 3 =16). Functional neurological disorder was classified by EDSS as mild, moderate or severe. For EDSS and OMDS, scores ≤ 6 for independent patients and scores above 6 for dependent patients were considered. The Kappa statistic was used to verify the level of agreement between the instruments (p-value≤0.05). **Results:** The sample consisted of 29 women and 10 men, with a mean age of 53.1 years (SD ± 12.2), ranging from 28 to 81 years. At EDSS, Group 1 presented 38.46% of mild disability, 46.15% of moderate disability and 15.38% of severe disability; Group 2 exhibited 90% mild and 10% moderate disability; Group 3 revealed 93.75% mild and 6.25% moderate disability. The results of the two scales indicated that in Group 1, 61.54% were independent in walking, and 38.46% were dependent on walking. In both Group 2 and Group 3, individuals presented independence for walking. The Kappa value showed a weak agreement between the two assessment instruments (K=0.07 and p=0.11). **Conclusion:** The evaluation of functional neurological incapacity allowed to identify patients who, although they do not exhibit TSP/HAM in a defined way, have reduced functional competences of minimal to moderate disability, as in the EDSS findings, suggesting the need for an early evaluations of all HTLV-1 carriers.

Key words: HTLV-1, HTLV-1 associated myelopathy; Functional disability.

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APPLICATION OF SPECIFIC NEUROLOGICAL DISABILITY SCALE IN HTLV-1 CARRIERS ACCORDING TO DEGREE OF NEUROLOGICAL INVOLVEMENT

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Background: The human T-lymphotropic virus 1 (HTLV-1) is a Deltaretrovirus that is associated with Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (TSP/HAM), a disease characterized by slowly progressive evolution of neurological impairment. The TSP/HAM predominantly affects the spinal cord and the most common neurological manifestations include decreased strength, increased tendon reflexes and muscle tone, presence of clonus and impairment of the functional systems of sensitivity and sphincters. Multiple aspects regarding the evolution, disability profile and therapeutic options still remain obscure due to the lack of an adequate tool to evaluate this neurological condition. To describe the results of the application of the scale of neurological disability at the Institute of Clinical Research Evandro Chagas (EIPEC-2) in HTLV-1 patients attending the outpatient clinic of the Tropical Medicine Center of the Federal University of Pará, Brazil. **Methods:** Cross-sectional study of 39 patients with positive antybody dectection for HTLV and for HTLV-1 proviral DNA by real time PCR between March and June 2017. These individuals were divided into three groups in descending order of neurological involvement, according to the updated proposal for diagnostic criteria to TSP/HAM: Definitive (Group 1=13); Probable (Group 2=10); Possible (Group 3=16). EIPEC-2, a scale developed exclusively for evaluation of the clinical progression of HAM / TSP, covers ranges from 0 to 29, with 17 possible points for motor score, 3 for spasticity, 4 for sensory evaluation and 5 for score of the sphincters, being higher scores indicative of more severe neurological impairment. A p-value ≤0.05 for statistical significance was considered. **Results:** There was a predominance of 74.4% female patients with mean age of 52 years (SD ± 13.2), but not statistically significant (p = 0.366), when compared to the male group (56.3 ± 8, 3 years old). Groups 1, 2 and 3 presented, respectively, the following scores on the scale: 16.3 ± 5.3; 6.6 ± 4.1; 4.6 ± 3.7. Regarding the subsection of gait in the motor score, Group 1 presented a 30.77% of need of support to walking and 69.23% use of a wheelchair as a help for locomotion. Both Group 2 and Group 3 presented a reduced range of individuals who needed ambulatory support (10% and 6.25%, respectively), and the others were independent for gait. **Conclusion:** The evaluation of neurological functional disability by EIPEC-2 demonstrated consistency in score scores according to the degree of neurological involvement of each group evaluated. Therefore, the use of this specific scale is suggested by the need for an early measurement of TSP/HAM.

Key words: HTLV-1, HTLV-1 associated myelopathy; Functional disability.

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EVALUATION OF THE PATELLAR REFLEX IN PATIENTS WITH HTLV-1 ACCORDING TO THE DEGREE OF NEUROLOGICAL INVOLVEMENT

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Background: Human T-lymphotropic virus 1 (HTLV-1) is a Deltaretrovirus associated with tropical spastic paraparesis / HTLV-1 associated myelopathy (TSP/HAM), a progressive viral immune-mediated disorder characterized by slow and progressive evolution, which can lead to a syndrome manifested by decreased strength and sensory impairment, presence of clonus and Babinski signal, sphincter dysfunction and hyperactived tendon reflexes and muscle tones. The patellar reflex is a deep tendon reflex mediated by the L2 and L4 nerve roots, mainly L4, which is critical in the neurological motor system evaluation. To describe the evaluation of the patellar reflex in patients with HTLV-1 treated at the outpatient clinic of the Tropical Medicine Center of the Federal University of Pará, Brazil. **Methods:** A cross-sectional study was carried out between March and June 2017 of 39 patients with positive results for HTLV antibodies and confirmation of HTLV-1 infection by molecular biology methods. The patients were categorized into three groups in descending order of neurological involvement according to the updated proposal for diagnostic criteria of TSP/HAM: Definitive (Group 1), Probable (Group 2) and Possible (Group 3). The participants were submitted to neurological evaluation with the evalution of bilateral patellar reflex testing, using the reflex hammer and the graduation according to Campbell: 0 (absent), +1 (trace or decreased response), +2 (normal), +3 (brisk) and + 4 (markedly hyperactive). The patient was asked to be relaxed in the sitting position with eyes closed before the examination and the evaluator perused the tendon point firmly and observed the extension of the knee. **Results:** The sample consisted of 29 women and 10 men, with mean age of 53.1 years (SD ± 12.2), ranging from 28 to 81 years. In Group 1, consisting of 13 individuals, 84.62% presented hyperactive patellar reflex, 7.69% brisk and 7.69% absent. In Group 2 was formed by 10 patients, 80% presented brisk reflex (increased but not necessarily in pathological degree) and 20% hyperactive reflex. The Group 3 was composed of 16 subjects and most of them (87.5%) presented normal patellar reflex and 12.5% decreased reflex. **Conclusion:** The evaluation of tendon reflexes allowed to identify patients who, although do not exhibit TSP/HAM in a defined way, have initial neurological alterations similar to those that already present the disease. Therefore, it is suggested that the neurological manifestations related to HTLV-1 be measured early for appropriated and immediated therapeutic targeting.

Key words: HTLV-1, HTLV-1 associated myelopathy; Neurological disorders.

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RADIOGRAPHIC ASPECTS IN INDIVIDUALS INFECTED BY HTLV-1 WITH COMPLAINT OF JOINT PAIN

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Background: Previous studies have associated HTLV-1 with auto immune rheumatic disorders such as rheumatoid arthritis, systemic lupus erythematosus and Sjogren syndrome, but recent epidemiologic and clinic data have contested this association. Alternatively the occurrence of joint manifestations in patients infected with HTLV-1 is well documented. However the clinical and radiographic findings related the HTLV-1 associated arthropathy are not established. In this study we evaluated radiographic changes in patients with joint pain associated to HTLV-1. **Methods:** Conventional x-rays were performed in 51 HTLV-1 infected subjects who present complaints of joint pain in the knees, hips and feet / ankles. **Results:** The mean age of the patients was 59 +/- 8.9 years and 80% were female. Regarding the clinic/ neurologic status, 26 (51%) patients were HTLV-1 carriers (HC), while 25 (49%) had diagnosis of probable or defined HTLV1 associated myelopathy or tropical spastic paraparesis (HAM/ TSP). The most common pattern of joint involvement was the symmetric polyarticular identified in 33 (65%) of the patients, followed by asymmetric oligoarticular in 8 individuals (15%). Among the 51 patients, 42 (82%) presented complaints of joint pain in the knees, 24 (48%) in the hips and 33 (65%) in the feet / ankles. The main radiographic findings in the joints were reduction of joint space, osteophytes and enthesophytes, with a frequency of 41%, 64% and 36%, respectively, in the knees; 8%, 4% and 54%, respectively, in the hips; and, 3%, 18% and 82%, respectively, in the feet / ankles. No difference in this findings were found when HTLV-1 carries were compared with HAM/ TSP ($p > 0,05$). **Conclusion:** Entesopathy, represented by the presence of enthesophytes, was the most frequent finding. HTLV-1associated artropathy is characterized clinically by simetric polyarthralgia and the main radiographic find is entesopathy, an abnormality that has been observed in other inflammatory artropathies.

Key words: HTLV-1; radiocraphic aspects; joint pain.

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ONABOTULINUMTOXIN TYPE A IMPROVES LOWER URINARY TRACT SYMPTOMS AND QUALITY OF LIFE IN PATIENTS WITH HUMAN T CELL LYMPHOTROPIC VIRUS TYPE 1 ASSOCIATED OVERACTIVE BLADDER.

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Background: Human T-lymphotropic virus type 1 (HTLV-1) is known to cause HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia. Urinary symptoms are observed in the majority of patients with HAM/TSP and are also observed in patients who do not fulfill the criteria for HAM/TSP. Up to now, there´s no specific treatment for HTLV-1 patients and we only have to deal with the disease´s symptoms and minimize complications, trying to improve health related quality of life (QoL). Urinary dysfunction presents mainly as overactive bladder, characterized by urgency, incontinence, nocturia and frequency. Moreover, bladder arreflexia/hypocontractility is also observed with limitations to eliminate the urine and fail to void. To evaluate the efficacy of the onabotulinum toxin type A in the treatment of HTLV-1 associated overactive bladder and its impact on QoL. **Methods:** Series of cases with 10 patients with overactive bladder refractory to conservative treatment with anticholinergic or physical therapy. Of the 10 cases 7 had HTLV-1 associated myelopathy and 3 had only neurogenic bladder. They were treated with 200Ui of onabotulinumtoxin type A intravesically and were evaluated by overactive bladder symptoms score (OABSS) at 30 and 90 days after treatment and when OABSS returned to previous score. King´s Health Questionnaire were applied before and 30 days after treatment. **Results:** The mean (SD) of the age was 52 + 14.5 years and 60% were female. All of them had confirmed detrusor overactivity on urodynamic study. The median and range of the OABSS was 13 (12-15) before therapy and decreased to 1.0 (0-12) on day 30 and to 03 (0-14) on day 90 ($p<0.0001$). There was a significant improvement in 8 of the 9 domains of the King´s Health Questionnaire after the intervention. Hematuria, urinary retention and urinary infection were the complications observed in 3 out of 10 patients. The mean time to request retreatment was 465 days. The Onabotulinum toxin type A intravesically reduced the OABSS with last long effect and improved the quality of life of HTLV-1 infected patients with severe overactive bladder. **Conclusion:** Onabotulinum toxin type A is effective in patients with neurogenic bladder associated to HTLV-1 and is a good option in patients refractory to anthicolinergic drugs.

Keywords: overactive bladder, onabotulinum toxin, HTLV-1.

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THE CLINICAL EVOLUTION OF THE URINARY DYSFUNCTION IN HTLV-1 INFECTED PATIENTS

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Background: The Human T Cell Lymphotropic Virus Type 1 (HTLV-1) is the causal agent of HTLV-1 associated myelopathy/Tropical Spastic Paraparesis (HAM/TSP). It is well known the urinary symptoms are associated with damage of neurological system. However, the is a lack of studies about the level of injury of the urinary dysfunction and the relationship between the degree of neurological injury with urinary symptoms. To describe the clinical evolution of urinary dysfunction associated to HTLV-1 infection. **Methods:** These are preliminary data of a cohort study with 143 HTLV-1 infected patients with urinary dysfunction evaluated between 2011 and 2017, whom will be followed up to 2019. The diagnosis of HTLV-1 infection was made by ELISA and confirmed with Western Blot. The patients were evaluated by the overactive bladder symptoms score (OABSS) and bladder diary every 6 months, and by at least 02 urodynamic studies in different time points. All patients were in use or have received anticholinergic drugs. The followed endpoints were considered: persistence of overactive bladder, change for detrusor hypocontractility, development of bladder areflexia or progression from probable HAM/TSP (neurogenic bladder) to HTLV-1 associated myelopathy (HAM/TSP). **Results:** 137 patients presented with urinary complaints. The mean of the age of the patients was 55 + 12.3 years, 108 (79%) were female and 44 (32%) had confirmed myelopathy. At the time of entry in the study 128 (93%) had OAB in the urodynamic study and 18 (13%) presented bladder impaired contractility. After the mean follow-up of 4.5 ± 1.3years, 105 (77%) of the patients maintained the same urinary status, 31 (23%) worsened the OABSS and 26 (19%) developed bladder impaired contractility. Four patients (2.1%) developed low bladder compliance and hydronephrosis and 3 (2.2%) patients required aggressive surgical treatment (bladder augmentation). The majority of the patients didn´t modified the urinary status and from those without myelopathy, none developed this form of disease. The exacerbation of overactive bladder and bladder impaired contractility were the main findings regarding progression of the urinary symptoms. **Conclusions:** Overactive bladder is the main clinical manifestations of urinary dysfunction in HTLV-1 and, in a short period of time, impairment of bladder contractility is the main complication of the disease.

Key words: HTLV-1; urinary dysfunction; HAM/TSP

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PREVALENCE OF SEXUAL DYSFUNCTION AMONG WOMEN INFECTED WITH HUMAN T CELL LYMPHOTROPIC TYPE 1 VIRUS (HTLV-1) AND RELATIONSHIP WITH NEUROLOGICAL IMPAIRMENT AND PRO-VIRAL LOAD

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Background: Neurologic injury of the spinal cord is the main pathologic finding in patients with HTLV-1 associated myelopathy or tropical spastic paraparesis (HAM/TSP). This may lead to neurogenic bladder and erectile dysfunction in males. Sexual dysfunction (SD) in women is well documented in the general population and our hypothesis is that HTLV-1 infected women have more SD than non-infected controls, and that this disorder is higher in those who have HAM/TSP than in HTLV-1 carriers (HC). To determine the prevalence of SD among HTLV-1 infected women and it's relationship with neurological impairment and pro-viral load. **Methods:** Cross-sectional study comparing the frequency of SD in 70 HTLV-1 infected women (cases) with 70 age-matched (± 5 years) seronegative blood bank donnors (controls). Cases were from the Multidisciplinary Outpatient Clinic of the University Hospital (HUPES, UFBA) and controls from the HEMOBA. Patients answered a questionnaire for sexual symptoms and the female sexual function index (FSFI) was determined. Moreover the degree of neurological impairment and pro-viral load were evaluated. **Results:** The mean age of the 49 infected women was 42.5 ± 8.2 years and of the 44 seronegative women was 32 ± 9.8 years ($p<0.001$); 29 infected women (59.2%) were sexually satisfied when compared to 43 controls (97.7%) ($p <0.001$), 25 infected (51%) had gynecological surgery while only 8 controls (18.2%), ($p<0.001$), 25 infected (51%) had urinary loss compared to none of the control group ($p <0.001$). The prevalence of SD was 76.4% in the cases and 21.7% in the controls ($p <0.001$). According to the FSFI, the Desire ($p <0.001$), Excitation ($p <0.001$), Lubrication ($p <0.001$), Sexual Satisfaction ($p <0.001$), Orgasm ($p <0.001$) and Pain ($p <0.001$) were lower in those with HTLV-1 than in the control. The domains Excitation ($p <0.05$), Lubrication ($p <0.05$) and Orgasm ($p <0.05$) were lower in those with HAM/TSP than in HC. The SD were more frequent in patients with HAM/TSP but the correlation between the degree of neurological impairment and SD ($R=0.33$, $p <0.01$), and between pro-viral load and SD ($R=0.38$, $p <0.001$) was only weak and moderate respectively. **Conclusion:** The SD is more frequent in HTLV-1 infected women than in seronegative controls but in addition to neurologic involvement, others factors related to the virus infection may play a role in the SD associated to HTLV-1 infection.

Key words: HTLV-1; sexual dysfunction; neurological impairment; proviral load

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FUNCTIONAL CAPACITY ASSESSMENT OF HUMAN T CELL LYMPHOTROPIC VIRUS CARRIERS IN NORHTEAST OF AMAZONIA

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Background: The Human T cell Lymphotropic Virus is a retrovirus with low pathogenicity and long term latency, which is usually associated to Adult T cell Leukemia/Lymphoma and to a neurological disease named HTLV-Associated Myelopathy/Tropical Spastic Paraparesis. Four subtypes are currently known, but the one related to harmful illnesses is HTLV-1, leading to neoplasic and inflammatory disesases; here we are considering also neurological, musculoskeletal and rheumatologic manifestations, which usually influence motor function and quality of life of these patients. To assess functional capacity of patients infected with Human T cell Lymphotropic Virus. **Methods:** The study design is observational, descriptive, analytical and transversal. The research was developed with 53 HTLV infected individuals from both gender, followed at Tropical Medicine Center, in the city of Belém, State of Pará, Brazil. Each patient was evaluated once with one instrument: a functional measurement scale, the Functional Independence Measure scale. **Results:** Most of carriers were women, with a range of infection of 5 years, and were, according to functional capacity, mostly independent on their daily living, instrumental and occupational activities, even in the presence of sensory-motor complaints. A slight loss in activities requiring greater demand of the lower limbs was noticed, especially in more complex tasks using the whole chain muscle, such as walking and climbing stairs. Complaints about sphincter dysfunction were also reported, so we must give attention to this because recent studies have shown that sphincter dysfunction is one of the first signals of disease progression and could be considered an early symptom of myelopathy. **Conclusions:** Most of the 53 patients were independent on their motor function, although almost all of them had any sensory-motor complaints, but with a few limitations. Those with complaints related to severe disability were an exception. Lost on sphincter dysfunction must be followed due to the possibility of future motor impairment.

Key words: HTLV-1; HAM/TSP; functional capacity

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HTLV-1 PROVIRAL LOAD IN CEREBROSPINAL FLUID MAY NOT BE A GOOD MARKER TO DIFFERENTIATE ASYMPTOMATIC CARRIERS WITH HIGH PROVIRAL LOAD IN BLOOD FROM HAM/TSP PATIENTS

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Background: Individuals with HTLV-1-Associated Myelophile or Tropical Spastic Paraparesis (HAM / TSP) may present with motor alterations, which may have repercussions without postural balance and consequent risk of falls. Objective to compare the balance of individuals with HAM / TSP and healthy individuals. **Method:** A cross-sectional study of individuals with HAM / TSP, attended at a referral Center. Excluding those with lower limb amputation, pregnancy, psychiatric disorders, rheumatic or orthopedic diseases, other associated neurological disorders, and those who are difficult to evaluate the evaluation instruments used. A healthy group was recruited for a comparative group, matched by sex, age and level of schooling. Sociodemographic and clinical data were collected and an equilibrium evaluation was performed using the Berg Balance Scale (BBS). The project was approved by the Research Ethics Committee of UCSal under CAAE 49634815.2.0000.5628. A $p < 0.05$ was considered more statistically significant. **Results:** A total of 42 subjects were selected, 29 (69%) with HAM / TSP and 13 from the comparative group, being 69% female, 45.2% married, and 47.6% brown. It was found that the individuals with HAM / TSP obtained a median and interquartile range 40 (36-48) points in BBS and those in the comparative group 55 (55-56) points in BBS. When comparing the two groups, in relation to the balance, we observed a statistically significant difference ($p < 0.001$). **Conclusion:** Individuals with HAM / TSP found significant balance according to the BBS in relation to healthy individuals, which may explain the presence of risk of falls in population.

Key-words: Postural balance; tropical spastic paraparesis; HTLV-1, HAM/TSP.

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BALANCE IN INDIVIDUALS WITH HTLV-1 ASSOCIATED MYELOPATHY OR TROPICAL SPASTIC PARAPARESIS (HAM/TSP):A SECTIONAL STUDY

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Background: Individuals with HTLV-1-Associated Myelophile or Tropical Spastic Paraparesis (HAM / TSP) may present with motor alterations, which may have repercussions without postural balance and consequent risk of falls. Objective: to compare the balance of individuals with HAM / TSP and healthy individuals. **Method:** A cross-sectional study of individuals with HAM / TSP, attended at a referral Center. Excluding those with lower limb amputation, pregnancy, psychiatric disorders, rheumatic or orthopedic diseases, other associated neurological disorders, and those who are difficult to evaluate the evaluation instruments used. A healthy group was recruited for a comparative group, matched by sex, age and level of schooling. Sociodemographic and clinical data were collected and an equilibrium evaluation was performed using the Berg Balance Scale (BBS). The project was approved by the Research Ethics Committee of UCSal under CAAE 49634815.2.0000.5628. A $p < 0.05$ was considered more statistically significant. **Results:** A total of 42 subjects were selected, 29 (69%) with HAM / TSP and 13 from the comparative group, being 69% female, 45.2% married, and 47.6% brown. It was found that the individuals with HAM / TSP obtained a median and interquartile range 40 (36-48) points in BBS and those in the comparative group 55 (55-56) points in BBS. When comparing the two groups, in relation to the balance, we observed a statistically significant difference ($p < 0.001$). **Conclusion:** Individuals with HAM / TSP found significant balance according to the BBS in relation to healthy individuals, which may explain the presence of risk of falls in population.

Key-words: Postural balance; tropical spastic paraparesis; HTLV-1, HAM/TSP.

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INCIDENCE OF KERATOCONJUNCTIVITIS SICCA (KCS) ASSOCIATED WITH HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1)

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Background: Human T cell lymphotropic virus type 1 (HTLV-1) was identified in 1980. Many other diseases have been associated with HTLV-1, such as polymyositis, sinusitis, thyroiditis, bronchial alveolar pneumonia, Sjörgren's Syndrome, indicating a multisystemic involvement in this infection. In order to determine the incidence of Keratoconjunctivitis sicca in HTLV-1 infected patients in Salvador Bahia, a transversal study was conducted on 98 HTLV-1 infected patients between December 2005 and June 2017. **Methods:** The ophthalmological examination included visual acuity measurement, ocular motility, biomicroscopy of the anterior and posterior chambers, intraocular pressure and evaluation of lachrymal secretion. Evaluation of tear secretion was performed by BUT (break-up time), Rose Bengal and Schirmer I Tests. The Rose Bengal test was performed with 0.1% solution Rose Bengal staining and was considered pathological when the total score was higher than three points (Van-Bijsterveld score). Scores of ≤10 seconds for break-up time and ≤5 mm for Schirmer I test were defined as abnormal. Diagnosis of KCS was based upon the presence of symptoms and at least two out of three positive tests.Statistical analysis was performed using the Epi-Info software, version 7.0, and the association between variables were analyzed with the level significance adopted was 0,05. **Results:** After informed consent, 98 HTLV-1 positive individuals were enrolled in this study. Most patients described themselves as white (51 %) or mulatto (38 %). The majority (53%) had not finished primary school. Regarding their marital status, 35 % were single and 4% married. Most of the patients were women (72 %), a mean age of 48 (± 15) years-old. Observation verified 38 (39%) out of 98 patients with keratoconjunctivitis sicca. The incidence of Keratoconjunctivitis sicca was significantly higher among the TSP/HAM patients (54,5 %) and hight level of proviral load (115066 ± 130701 copies/ml). **Conclusion:** This study showed a high incidence of keratoconjunctivitis sicca (39%), similar to a prevalence study conducted in Brazil and Martinique. The correlation of CPV with the diagnosis of KCS suggests that this measure serves as a basis for a more frequent follow-up of these patients. We recommend that HTLV-1 infected individuals be regularly followed up with periodic eye examinations that allow the early diagnosis of these ocular pathologies and consequently have an improvement in quality of life.

Key words: HTLV-1; HAM/TSP; keratoconjunctivitis sicca

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EFFECTS OF PHYSIOTHERAPY IN THE TREATMENT OF NEUROGENIC BLADDER IN PATIENTS INFECTED WITH HUMAN T-LYMPHOTROPIC VIRUS 1 (HTLV-1)

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Background: Human T-lymphotropic virus (HTLV-1) is the etiological agent of HTLV-1–associated myelopathy or tropical spastic paraparesis (HAM or TSP). Although it only occurs in 2% of the infected individuals, other isolated or assorted syndromes may occur in a large percentage of HTLV-1–infected subjects. Urinary complaints are present in virtually all patients with HAM or TSP and occurs in around 30% of HTLV-1–infected individuals. The most common urodynamic finding in HTLV-1– infected patients is detrusor overactivity (DO). Later, detrusor-sphincter dyssynergia (DSD) or detrusor are- flexia (DA) may develop, with the two dysfunctions possibly coexisting in HTLV-1–infected patients. These dysfunctions may cause severe and irreversible consequences to the lower urinary tract. Moreover, neurogenic bladder (NB) is the principal cause of the urinary symptoms in HTLV-1 infected individuals. **Objective:** To evaluate the efficacy of physiotherapy for urinary manifestations in patients with human T-lymphotropic virus 1–associated lower urinary tract dysfunction. **Methods:** An open clinical trial was conducted with 21 patients attending the physiotherapy clinic of the Hospital Universitário, Bahia, Brazil. Combinations of behavioral therapy, perineal exercises, and intravaginal or intra-anal electrical stimulation were used. **Results:** The mean age was 54 $\pm$ 12 years and 67% were female. After treatment, there was an improvement in symptoms of urinary urgency, frequency, incontinence, nocturia, and in the sensation of incomplete emptying ($P < .001$). There was also a reduction in the overactive bladder symptom score from 10 $\pm$ 4 to 6 $\pm$ 3 ($P < .001$) and an increase in the perineal muscle strength ($P < .001$). The urodynamic parameters improved, with reduction in the frequency of patients with detrusor hyperactivity from 57.9% to 42.1%, detrusor-sphincter dyssynergia from 31.6% to 5.3%, detrusor hypocontractility from 15.8% to 0%, and detrusor areflexia from 10.5% to 0%, with positive repercussions in the quality of life in all patients. **Conclusion:** Physiotherapy was effective in cases of human T-lymphotropic virus 1–associated neurogenic bladder, reducing symptoms, increasing perineal muscle strength, and improving urodynamic parameters and quality of life.

Key words: HTLV-1; physiotherapy; treatment; neurogenic bladder.

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SEROPREVALENCE OF HUMAN T-LYMPHOTROPIC VIRUSES (HTLV) INFECTION AMONG BLOOD DONORS IN BENIN

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Background: HTLV transmission can occur through blood transfusion, sexual contact and via breast-feeding. Considering that the highest risk of infection is associated with the transfusion of untested packed red cells, a major challenge of the Ministry of Health in Benin is the provision of high quality blood products that meet World Health Organization (WHO) standards that ensure blood safety. The present study was designed to assess the seroprevalence of HTLV among blood donors in Benin. **Methods:** A cross-sectional study was carried out by screening for HTLV using enzyme-linked immunoassay procedures in samples obtained from six blood banks located throughout the provinces of Benin. **Results:** The study population consisted of 2,035 blood donors. Screening procedures found 12 blood donors with a positive result for HTLV infection, while the sera of seven blood donors was considered borderline, i.e. indeterminate serology, providing an overall prevalence of 0.93%. No blood donors with positive serology for HTLV tested positive for the other retroviruses previously screened by blood banks. All positive cases had not previously received blood transfusions. **Conclusion:** Our result indicating the importance of including HTLV screening in all blood banks in Benin for the prevention and control of the infection.

Key words: HTLV-1; seroprevalence; blood donors

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EPIDEMIOLOGICAL PROFILE OF PATIENTS WITH HUMAN T-CELL LYMPHOTROPIC VIRUS ASSOCIATED KERATOCONJUNCTIVITIS SICCA

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Background: Keratoconjunctivitis sicca (KCS) is a multifactorial disease of the ocular surface that results in ocular discomfort, visual disturbance and tear film instability. KCS is part of the clinical spectrum of human T-cell lymphotropic virus (HTLV) infection, being endemic in the city of Salvador, Bahia. **Methodology:** A cross-sectional study was carried out analyzing the epidemiological profile of a sample of 98 patients attended at the HTLV Center at the Bahian School of Medicine, 38 of them with a confirmed diagnosis of KCS. Diagnostic confirmation was obtained by Shirmer 1, break-up time and rose Bengal test, where 2 of the 3 should be altered. A complete ophthalmologic evaluation was also performed in each patient. Statistical analysis was performed using epi-info software, version 7.0. to estimate the risks of KCS in patients with HTLV. **Results:** Of the 98 patients, 71 were female and 27, male. Of these, the prevalence of KCS among women was 39.4% and in men, 37%. Regarding marital status, the groups evaluated were: single (N = 44), married / stable union (N = 34), divorced (N = 4) and widowed (N = 11). Of these, the prevalence of KCS was higher in the group of widowers (73.3%), followed by singles (36.4%) and married (26.5%). Regarding self-referenced color, 9 patients were considered white, 50 brown, 37 black and 2 yellow. The prevalence of KCS in the white group was 44.4%, while in the non-white group it was 42.6%. The group with less than 10 years of schooling presented 38.4% of KCS prevalence, the group with less than 15 years of schooling was 34.28% and the group with 15 years or more of study was 33.3%. **Conclusion:** According to the data analyzed, the female sex presented a 1.06 more chance of developing CCS in relation to the male sex. Single patients present 1.37 more chances to develop CCS when compared to married patients. The estimated risk of developing SCC was 1.04 times higher in the white group than in the non-white group. It was also observed that the estimate of the risk of developing CCS was inversely proportional to the study years. Comparing patients with less than 10 years of study with those with more than 15 years of study, the first one presented 1.15 times more chances of developing CCS.

Key words: HTLV-1; keratoconjunctivitis sicca; epidemiological profile

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DETECTION OF HUMAN T-LYMPHOTROPIC VIRUS (HTLV) IN CERVICAL MUCUS OF UNIVERSITY STUDENTS

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Background: Human T-lymphotropic virus (HTLV) infects about 20 million people around the world and 2.5 million of these are located in Brazil. The infection is associated with development of serious diseases. However, as the infection presents a slow development, it tends to show late clinical manifestations as well. The virus is transmitted by horizontal and vertical disease transmission. Paiva (2016) mentions a possible correlation between viral load in peripheral blood and the presence of the virus in cervical mucus. Zunt et al. (2002) described the presence of HTLV's genetic material in cervical mucus in 68% of 63 HTLV-1-infected sex workers. **Methods:** All collected data were stored in a Microsoft Excel 2010 spreadsheet. Serum samples were tested for HTLV-1/HLTV-2 antibodies by means of ELISA method. Cervical mucus samples were tested by nested PCR of pX region and then submitted to electrophoresis in 2% agarose gel. Samples with amplification of a 159 bp region were submitted to genotyping with restriction fragment length polymorphism (RFLP) to distinguish HTLV-1 and HTLV-2. **Results:** 196 cervical mucus samples of students from Belém city (state of Pará) were tested but none of them was found to be HTLV positive. The age variation in this research was from 17 to 55 years old with average of 26. 69.39% of students declared to be in a stable relationship and 55.38% declared not to make frequent use of condoms. The age variation for the beginning of sexual life was from 11 to 32 years old with average of 18. **Conclusion:** HTLV's proviral material was not detected in the tested cervical mucus samples. The non-detection of HTLV's proviral material in cervical mucus is probably due to low average of age of the enrolled students, which is below the common average found in other studies and might have correlation with late seroconvertion.

Key words: Sexually transmitted infection, HTLV, Public health.

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MODERATE ENDEMICITY OF THE HUMAN T-CELL LYMPHOTROPIC VIRUS INFECTION IN METROPOLITAN REGION OF BELÉM CITY, NORTHERN OF BRAZIL

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Background: Human T-cell leukemia virus type 1 (HTLV-1) infection is highly prevalent in NorthEast and Norte of Brazil. This study evaluated, for the first time, by a based population strategy at the highly density Metropolitan area of Belém, with an estimated population of 3 million of people. **Methods:** Individuals older than 18 years, workers or passerby of the largest free fair (Ver-o- Peso) and a large square of Belém city (Republic Square) between November 2014 and November 2015. Those whom accepted to participate, after written informed consent, were screened using anti-HTLV-1/2 antibodies detection for screening (Gold ELISA-REM), and those positives were tested with molecular confirmation. **Results:** A total of 1059 individuals were investigated, of which 1019 (96%) were resident in the metropolitan area of Belém. Twenty-one subjects (2%) anti-HTLV-1/2 antibodies were detected, fifteen (1.4%) were confirmed HTLV-1, five cases (0.5%) as HTLV-2 and in one case no proviral DNA was detected. In general, the HTLV-1-positive cases showed mean of age 46.4 years and those with HTLV-1 with (mean of age 57.2 years) versus 46.2 years of age in those non-infected cases (p=0.001). The prevalence of infection increases proportionately to the age range of women, but not among men. The infection was highlighted in 2.7% of people with a family income less than or equal to a minimum wage (U $ 300) (p = 0.0114). Three of the ten clinically investigated HTLV-1 carriers already had some infection-related symptom. Intrafamilial transmission was investigated in six families, all stainded virus transmission. **Conclusion:** We observed a moderate (2%) prevalence of HTLV infection in the adult population of the metropolitan region of Belém. In addition, highest prevalence is noted in older women and those with low income. This endemic is possibly due to family aggregation, sexual and vertical transmission of HTLV-1 infection.

Key words: HTLV-1; HAM/TSP; endemicity

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FACTORS ASSOCIATED WITH HTLV INFECTION IN PARTURIENTS IN SALVADOR BAHIA

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Background: Salvador (Bahia stated) is one of the cities with a high percentage of HTLV-1 infection in Brazil. Sexual and vertical transmission have been identified as routes for the spread of HTLV and the occurrence of diseases associated with this virus, as an Adult T-cell leukemia/lymphoma (ATL) and infective dermatitis. The present study evaluated the factors associated with the prevalence of HTLV I/II in parturients of two maternity hospitals in Salvador Bahia. **Methods:** A cross-sectional study was conducted with parturient women, whose deliveries occurred in two maternity hospitals in Salvador-Bahia between April 2016 and June 2017. Data on sociodemographic, obstetrical and clinical factors were collected by questionnaire and the presence of HTLV infection was determined by HTLVI/II antibodies by ELISA and confirmed by Western blot. A univariate and multivariate statistical analysis was used to evaluate the factors associated with HTLV infection. **Results:** 2,101 parturient women were studied. HTLV seroprevalence was 0.4% (95% CI: 0.2-0.7). The mean profile found was related to young women (mean age: 27.5 years), 75% living with a partner, 72.8% completing secondary school, 40.8% were housewives, and 45% with low family income. Seventy-four percent reported unprotected sexual practices, 17% using drugs, alcohol or smoking and 4% multiple sexual partners during pregnancy. Antenatal care service utilization was satisfactory (97%), large proportion of parturient initiated antenatal care in the first trimester of pregnancy (64.5%) and had six minimum visits (70%). Furthermore, in the clinical characteristics, there was a high prevalence of syphilis (4%) and a case of HIV-1/HTLV -1 coinfection is presented. The multiple regression model identified that the following factors were associated with HTLV seroprevalence in the study population: domestic violence event (OR 8.5, CI95%:1.9-37.5), deprivation of liberty history or their sexual partner (OR 8.0 IC95%:1.6-38.9), history of stillbirths (OR 9.8 IC 95%:1.9-51.9) and history of sexually transmitted infection (STI) in their partner (OR 109.9 IC 95%:12.1 – 980.6). **Conclusion:** The prevalence rate of 0.4% in HTLV parturients evidences persistence of infection in this population, and it is associated with vulnerability conditions and sexual risk behavior. Additionally, there is an independent association between stillbirth history and HTLV-1 infection. More studies are needed to assess trends in the rate of HTLV detection among pregnant women and in the pathogenic mechanisms in pregnancy outcomes.

Key words: HTLV-1; prevalence; parturients

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OCCURRENCE OF STRONGYLOIDIASIS IN HTLV-1 CARRIERS

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Background: Strongyloidiasis, an intestinal parasitic disease caused by nematodes of the genus Strongyloides. It is endemic in tropical and subtropical regions, especially in countries where sanitary conditions are precarious. Usually, S. Stercoralis infections are chronic and asymptomatic, and may persist for decades without being diagnosed. However, in individuals infected with human T-lymphotropic virus type 1 (HTLV-1) there is an increase of susceptibility of S. Stercoralis infection, progression to severe forms of strongyloidiasis and lower therapeutic response to the parasite. HTLV-1 is widely distributed worldwide with an estimate of 15-20 million infected people. In Brazil, HTLV-1 infection affects approximately 2.5 million people, but only few individual develop adult T-cell leukemia/lymphom or tropical spastic paraparesis/myelopathy. The aim of this study was to investigate the S. stercoralis infection and seraprevalence of IgG anti-S. stercoralis in HTLV-1 infected patients. **Methods:** An exploratory descriptive and cross-sectional epidemiological study was carried out from September 2014 to December 2016 at the Multidisciplinary Integrative Center for Patients with HTLV (CIMP-HTLV) of the Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil. The parasitological diagnosis was performed through three different parasitological methods, spontaneous sedimentation (SE), Baermann-Moraes (BM) and agar plate culture (CPA) from 161 patients, as well as the Immunoenzymatic Assay (ELISA) for detection of circulating IgG anti-S. stercoralis. **Results:** Of these patients 68.3% were female (mean age of 31.7% years, ranging from 15 to 76) and 46.1 % males (mean age of 51.0 years, ranging from 15 to 92 years). Only 1.9% (03/161) of these patients were infected with S. stercoralis. Other parasitic infections were also diagnosed: 1.9% (03/161) of Ascaris lumbricoides, 0,6% (01/161) of Schistosoma mansoni, 0,6% (01/161) of Trichuris trichiura and 0,6% (01/161) of Ancylostomidae. Sensitivity and specificity of serological diagnosis was 85.3% and 97,9%, respectively, the frequency of IgG anti-S. Stercoralis was 14,3% (23/161). The low rate of S. stercoralis infection probably reflects the control of HTLV-1 infection. Most of the patients have a low pro-viral load and systematically have medical care. Moreover, they had good sanitary conditions, 84.5% (136/161) a sewage network, 86.6% (139/161) paved streets, 96.6% (156/161) access to a bathroom with a hand sanitizer, 92.5% (149/161) potable water and 85.1% (137/161) drank filtered, boiled or mineral water. As for schooling, 60.3% (97/191) had not finished high school and had income of a monthly minimum wage. In spite of the difference between the S. stercoralis infection and seraprevalence of IgG anti-S. stercoralis, probably it reflects cross-reaction with other parasites, immunological memory of pass infections and /or low sensitivity to detect S. stercoralis infection by parasitological methods.

Keywords: Human T-lymphotropic virus 1. Strongyloides stercoralis. Diagnosis. Enzyme-Linked Immunosorbent Assay

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S. STERCORALIS AND HTLV-1 COINFECTED PATIENTS FROM THE SAME FAMILY

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Background: Strongyloidiasis is a parasitic disease caused by Strongyloides stercoralis, which affects around 100 million people worldwide. The most affected regions are tropical and developing countries, whose climate and low socioeconomic conditions favor infection, which tends to occur in a chronic and asymptomatic way. However, in individuals co-infected with the human T-lymphotropic virus type 1 (HTLV-1), there is an increased susceptibility to S. stercoralis infection, progressing to more severe forms of strongyloidiasis and lower therapeutic response. The aim of this study was to investigate the S.stercoralis infection and seraprevalence of IgG anti-S. stercolalis in HTLV-1 infected family coming from Baía de Camamu, Brazil. **Methods:** An exploratory descriptive and cross-sectional epidemiological study of active search which has been carried out from 2015 to 2017. The parasitological diagnosis was performed through three different parasitological methods, spontaneous sedimentation (SE), Baermann-Moraes (BM) and agar plate culture (CPA) from 16 patients, as well as the Immunoenzymatic Assay (ELISA) for detection of circulating IgG anti-S.stercoralis. The first approach to the family occurred when one of its members was attended at Multidisciplinary HTLV Center, Salvador and Bahia and was diagnosed with S. stercoralis hyperinfection. **Results:** Currently the family is made up of 16 members, 43.7% were female (mean age of 16,6 years, ranging from 04 to 64) and 56.3 % males (mean age of 19.0 years, ranging from 01 to 46 years). The parasitological diagnose demonstrated that 20,0% (03/15) were infected with S. stercoralis, 20,0% (03/15) of Ascaris lumbricoides, 33,3% (05/15) of Enterobius vermicularis, 66,7% (10/15) of Trichuris trichiura and 20,0% (03/15) of Ancylostomidae, 40,0% (06/15) of Giardia lamblia, Endolimax nana and Entamoeba coli, each. Being that 73.3% (11/15) of these patients are polyparasited. The frequency of IgG anti-S. Stercoralis was 71,4% (10/14). The high frequency of parasite infection probably reflects the socioeconomic and demographic conditions of this family. Of the sanitary conditions no member 100% (16/16) of the family have a sewage system, paved streets, access to the bathroom with a hand sanitizer and a toilet and access to drinking water. It has been reported that they sometimes drink unfiltered or boiled water. Regarding the level of schooling, no member has yet completed High School and the monthly income of up to one minimum salary. The frequency of S. stercoralis infection in this group, using serological methods, was about 5x greater than the parasitological methods ($p < 0.05$). This fact can be attributed to the intermittent release of larvae, reducing the sensitivity of the parasitological method, and the presence of cross-reactions with other helminths. Thus, the use of more sensitive parasitological methods, together with the search for antibodies, is a safer approach for the diagnosis and follow up of the treatment of strongyloidiasis.

Keywords: Human T-lymphotropic virus 1. Strongyloides stercoralis. Diagnosis. Enzyme-Linked Immunosorbent Assay

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HUMAN T-LYMPHOTROPIC VIRUS 1AA CIRCULATION AND RISK FACTORS FOR SEXUALLY TRANSMITTED INFECTIONS IN AN AMAZON GEOGRAPHIC AREA WITH LOWEST HUMAN DEVELOPMENT INDEX (MARAJÓ ISLAND, NORTHERN BRAZIL)

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Background: This cross-sectional study evaluated the prevalence of infection with human T-lymphotropic virus 1 and 2 (HTLV-1 and HTLV-2) in a population from the municipalities of Anajás, Chaves, São Sebastião da Boa Vista (SSBV) and Portel in the Marajó Archipelago and correlated these data with the epidemiological characteristics of the study population. **Methods:** A total of 1,899 biological samples were evaluated. The samples were screened for the presence of anti-HTLV antibodies using an enzyme-linked immunosorbent assay (ELISA), and infection was confirmed using conventional polymerase chain reaction (PCR), real-time PCR and nucleotide sequencing. **Results:** Eleven samples (0.58%) were seropositive for HTLV, but molecular analysis confirmed positivity in only two samples (0.11%). Nucleotide sequencing and phylogenetic analysis indicated that the two samples positive for HTLV-1 that were isolated in Chaves belonged to the Cosmopolitan subtype 1 (HTLV-1a) and Transcontinental subgroup (A). **Conclusion:** Our results confirmed the presence of Cosmopolitan Transcontinental HTLV-1 in the Marajó Archipelago, Amazon region, and revealed a lack of knowledge on the part of the population about infectious diseases, which increases the risk of dissemination of HTLV and other sexually transmitted infections.

Keywords: HTLV-1aA; Epidemiology; Marajó Island.

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CLINICAL-EPIDEMIOLOGICAL PROFILE OF HTLV-1 INFECTED INDIVIDUALS FOLLOWED IN A REFERENCE CENTER FROM THE SOUTHERN BAHIA

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Background: In order to know demographic and clinical-laboratory aspects of the HTLV infection in the southern region of Bahia. **Methods:** HTLV-1 infected individuals attended at "Centro de Referência em Prevenção, Assistência e Tratamento – CEPART" in Itabuna were evaluated from August 2015 to June 2016. This study was approved by CEP (CAAE registration: 22727114700005526). After explaining the objectives, application of the TCLE and structured questionnaire, samples of peripheral blood were collected from 55 HTLV-1 infected individuals and 116 not infected. The samples were processed in the "Laboratório de Farmacogenômica e Epidemiologia Molecular/LAFEM–UESC"; hematological and biochemical tests performed in two private clinical analysis laboratories from Itabuna; and immunological dosages were performed by LACEN. The parasitological exams were performed in "Laboratório de Parasitologia/LAPAR-UESC". The infected individuals were mostly women (82.70%), with low income and low level of formal education, similar to what is reported in other regions of the country and in the literature. Most of the infected individuals resided in the city of Itabuna, but 36.5% lived in 10 other cities located in the southern Bahia. Most individuals reported being asymptomatics. Ten (18.2% - 10/55) subjects reported complaints that could be associated with viral infection (such as foot numbness, leg weakness and difficulty walking). In laboratory tests, among those infected, a greater number of basophiles were observed and almost half of the individuals were parasitized. In addition, it was verified increased triglyceride levels in the infected group ($p = 0.04$). Besides, increased total cholesterol levels in HTLV-positive women were observed when compared to uninfected women ($p = 0.02$). As the nervous system has a high percentage of lipids in its composition, dyslipidemias may be related to viral pathogenesis. In addition, high cholesterol levels in infected women may be associated with a greater preponderance of this infection in this gender. However, this question remains to be clarified in later studies.

Key words: HTLV-1; clinical profile; epidemiological profile

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PREVALENCE OF BOWEL SYMPTOMS IN PATIENTS INFECTED WITH HUMAN T-LYMPHOTROPIC VIRUS 1 (HTLV-1)

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Background: In addition to HTLV-1 associated myelopathy or tropical spastic paraparesis (HAM/TSP), subjects with HTLV-1 infection present other neurologic manifestations as neurogenic bladder, erectile dysfunction and constipation. Constipation is a frequent symptom in patients with HAM/TSP, but the prevalence of bowel dysfunction mainly related to evacuation in HTLV-1 infected subjects and it's relationship with other neurologic manifestations have not been studied. **Objective:** To determine the frequency of bowel symptoms in HTLV-1 infected subjects and it's relationship with the degree of neurologic involvement. **Methods:** This is a cross-sectional study comparing bowel symptoms in HTLV-1 infected subjects followed at the HTLV-1 Multidisciplinary Clinic of the University Hospital (cases), with those observed in seronegative blood bank donors (controls). Patients answered a questionnaire, the Rome III Criteria and Bristol Scale were applied, and stool consistency was evaluated by the Bristol Stool Form Scale. The cases were classified in carriers (HC) patients with HAM/TSP and probable HAM/TSP (neurogenic bladder associated with HTLV-1). **Results:** Participants were 72 HTLV-1 infected individuals being 16 with HAM/TSP, 14 HAM/TSP probable and 42 HC and 72 controls. There was no difference between the groups regarding age and gender. The constipation was the most frequent complaint occurring in 27(38%) of the cases and in 11(15%) of the controls (P <0,01). However it was more frequently in HAM/TSP. The frequency of straining, lumpy or hard stools, sensation of anorectal obstruction/blockage, fewer than three defecations per week, flatulence, soilling, evacuation pain and bleeding were also higher between cases than controls (P <0,01) and were higher in patients with definitive or probable HAM/TSP than in HC. Evacuation effort, flatulence and evacuation pain were higher in HC than in controls. **Conclusion:** Constipation, straining, lumpy or hard stools, sensation of anorectal obstruction/blockage, fewer than three defecations per week, flatulence, soilling, evacuation pain and bleeding, are more frequent in HTLV-1 infected subjects than in seronegative controls. The prevalence of bowel symptoms was also higher in patients with HAM/TSP than in HC indicating that neurologic damage in the spinal cord due to HTLV-1 infection is the cause of play in important role in bowel symptoms.

Key words: HTLV-1; HAM/TSP; bowel symptoms

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ASSESSMENT OF THE LEVEL OF KNOWLEDGE OF PREGNANT WOMEN AND WOMEN OF CHILDBEARING AGE LIVING IN THE CITY OF SÃO PAULO ON HUMAN T-CELL LYMPHOTROPIC VIRUS (HTLV)

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Background: Human T-cell lymphotropic virus (HTLV) was the first discovered retroviral agent. The routes of transmission are the same as other retroviruses such as sexual activity, blood transfusion and breastfeeding. Breastfeeding is the most efficient route of transmission of the virus, and about 20% of infected infants develop diseases such as adult T-cell leukemia / lymphoma (ATLL). This study aimed to evaluate the degree of knowledge of pregnant women and women of childbearing age in the city of São Paulo regarding the infection caused by HTLV virus. **Methods:** A questionnaire was administered to 186 participants, pregnant or women of childbearing age, in which their knowledge regarding the prevention of sexually transmitted diseases, forms of transmission and public health issues was evaluated. **Results:** The age group of the study population had a predominance of women between the ages of 20 and 30 years and medium level schooling. STD screening is common in all pregnant women in the study, but it is not a common practice for women of childbearing age. It was verified that the studied population is not aware of the existence of the HTLV virus and does not make frequent use of the condom. It can be observed that most of the pregnant women believe that breastfeeding does not transmit diseases to the infants. Breastfeeding presented as one of the mechanisms of transmission of diseases less marked. This result shows that in addition to not knowing the HTLV virus, the interviewees have difficulty recognizing breastfeeding as a form of disease transmission. **Conclusion:** The women studied here do not demonstrate knowledge about the HTLV virus, but recognize the importance of implementing public policies for the prevention of the disease, such as the implantation of serology in the prenatal booklet of pregnant women.

Keywords: Retrovirus, HTLV, Women, Pregnant Women, Transmission Vertical.

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EVALUATION OF THE CERVICAL-VAGINAL ENVIRONMENT IN HTLV-1-INFECTED WOMEN

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Background: Human T-cell lymphotropic virus type 1 (HTLV-1) is endemic in several regions of the world, including Brazil. The prevalence of infection is higher among women and increases with age. The virus induces the production of inflammatory cytokines and the proviral load is implicated in the development of diseases associated with HTLV-1. Individuals infected with HTLV-1 may have ocular, oral, and xeroderma dryness. This study aimed to compare the cervical-vaginal environment of HTLV-1 infected and uninfected women through cytokine profile, lubrication index and cytopathologic findings. **Methods:** This is a cross-sectional study. Women were sequentially included during their medical consultation in the HTLV Center and gynecology clinic both located in EBMSP in Salvador. All volunteers underwent gynecological examination to collect cervical-vaginal samples. Quantification of cytokines in vaginal fluid was performed using the Cytometric Bead Array (CBA) Human Th1 / Th2 / Th17 kit. The proviral vaginal load was measured by real-time quantitative PCR (Polymerase Chain Reaction) and cervical-vaginal cytopathology by means of light microscopy. The assessment of vaginal lubrication was performed through the lubrication domain of the FSFI (Female Sexual Function Index) questionnaire. **Results:** A total of 112 women (63 infected and 49 not infected by HTLV-1) were evaluated. In relation to the cervical-vaginal cytopathological analyzes, there was no difference between the groups. Median lubrication rates were similar: 4.8 (3.6 - 5.4) in HTLV + and 4.8 (4.2 - 5.7) in the HTLV - group. About 52.6% of the HTLV + women evaluated had detectable vaginal proviral load, with a median of 62 (0-2057) / 106 cells (0.006%). For the quantification of cytokines in vaginal fluid, concentrations of IL-2 ($p=0,001$), TNF ($p=0,001$), IL-4 ($p<0,001$), IL-10 ($p=0,002$) e IL-17 ($p<0,001$) in cervical-vaginal fluid were significantly higher in HTLV-1 infected women than in the uninfected group. The level of IL-6 did not present statistical difference between the groups evaluated ($p = 0,1$). On the other hand, IFN-γ had a higher concentration in HTLV-1 non-infected women ($p <0,001$). **Conclusion:** Women infected with HTLV-1 have an inflammatory environment in the vaginal mucosa, characterized by elevated concentrations of Th1, Th2 and IL17 cytokines in vaginal fluid. However, no differences were found in the frequency and severity of cervical-vaginal cytopathologic changes or in vaginal lubrication among the groups evaluated.

Key words: HTLV-1; cervical-vaginal e nvironment; infected woman

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IL-17 AND IFN-γ PRODUCTION BY B LYMPHOCYTES AND ITS ASSOCIATION WITH LOW PROVIRAL LOAD IN PATIENTS WITH HTLV-1 ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS (HAM/TSP)

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Background: Recent evidence demonstrates that B lymphocytes are also capable of releasing cytokines such as IL-17 and IFN-γ and may contribute to the development of the inflammatory environment of Tropical Spastic Paraparesis / Myelopathy associated with HTLV-1 (HAM / TSP). Thus, the aim of this study was to analyze the phenotype of B lymphocytes in HTLV-1 carriers, investigating the cellular profile differences between HAM / TSP and asymptomatic carriers (AC) as well as its relation with the proviral load. **Methods:** PBMC samples from 28 patients were investigated, 11 HAM / TSP and 17 AC, attended at Oswaldo Cruz University Hospital (HUOC). Cells were maintained in RPMI medium, in the presence of phytohemagglutinin (PHA), and analyzed by detection of CD5 and CD19 surface markers and IFN-γ and IL-17 cytokines by flow cytometry (FACSCalibur-BD Biosciences). The proviral load was determined by qPCR using the protocol described by Costa et al, 2011 and a plasmid constructed in house as a positive control. Statistical analysis was done using GraphPad Prism 5.0 software. **Results:** The frequencies of B (CD19 +) and B-1a (CD19 + CD5 +) lymphocytes were similar between the HAM / TSP and AC groups ($p = 0.65$ and $p = 0.68$, respectively). Both B-lymphocytes and B-1a were found to produce IL-17 and IFN-γ on HTLV-1 infection. Patients with HAM / TSP had a higher frequency of IL-17 + B lymphocytes compared to AC ($p = 0.04$), What was not observed in B-1a lymphocytes ($p = 0.18$). Expression of IFN-γ was similar between the HAM / TSP and AC groups ($p = 0.60$ and $p = 0.85$, respectively), as well as the co-expression of IFN-γ and IL-17 cytokines ($p = 0.37$ and $p = 0.63$). It was observed that patients with HAM / TSP showed proviral load higher than AC ($p = 0.01$). In addition, negative correlations were observed between the proviral load and the frequency of CD19 + and B-1a B lymphocytes that co-expressing IL-17 and IFN-γ in the HAM / TSP group ($p = 0.03$; $r = -0, 66$, $p = 0.02$, $r = -0.62$, respectively). **Conclusion:** Thus, besides proving the production of proinflammatory cytokines by B lymphocytes from individuals infected by HTLV-1, these results may indicate that presence of this subpopulation may be related to a compensatory mechanism between the antiviral response and the protection against myelopathy. However, further studies are needed to investigate the role of these subpopulations in individuals infected with HTLV-1.

Key words: HTLV-1; lymphocytes B; proviral load; HAM/TSP; IL-17 and IFN-γ.

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EVALUATION OF TREG X TH17 RESPONSE IN PATIENTS DIAGNOSED WITH HTLV-1 ASSOCIATED MYELOPATHY/ TROPICAL SPASTIC PARAPARESIS (HAM/TSP)

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Background: HTLV is endemic in Brazil and it is associated with the development of Tropical Spastic Paraparesis/ Myelopathy associated with HTLV (HAM / TSP). Among the subpopulations of CD4 + T lymphocytes, Th17 and Treg may be involved in the development of HAM / TSP. In this context, the aim of this study was to analyze the phenotype of Th17 and Treg lymphocytes in HTLV-1 carriers, investigating the cellular profile differences between HAM / TSP and asymptomatic carriers (AC). **Methods:** PBMC samples were used from 28 patients, 11 HAM / TSP and 17 AC, attended at the University Hospital Oswaldo Cruz (HUOC). Cells were maintained in RPMI medium supplemented with 10% fetal bovine serum (FBS) in a 37°C humidified incubator with 5% CO, in the presence of phytohemagglutinin (PHA), and analyzed by detection of CD4 and CD25 surface markers, IFN-γ and IL-17 cytokines, and FoxP3 transcription factor by flow cytometry (FACSCalibur-BD Biosciences). Statistical analysis was done using GraphPad Prism 5.0 software. **Results:** Although there were no differences in the percentage of CD4+ T subpopulations studied between the HAM / TSP and AC groups, Th17 IFN-γ expression was observed in the HAM / TSP and AC groups, subdividing this population into Th17 producing and non-producing IFN-γ ($p= 0,76$ and $0,75$, respectively), in addition to the presence of Treg lymphocytes expressing IFN-γ (CD4 + CD25 + FoxP3 + IFN-γ +) in both groups ($p = 0.71$). There was a positive correlation between the frequencies of Treg and Th17 lymphocytes in the HAM / TSP group ($p = 0.0004$; $r = 0.87$), but did not remain in the AC group ($p = 0.72$, $r = 0.09$). In Th17 subpopulation expressing IFN-γ, it was observed that patients with HAM / TSP showed a positive correlation between the Treg and Th17 IFN-γ + lymphocytes ($p = 0.02$, $r = 0.59$), While between the Treg and Th17 IFN-γ-, this correlation was negative in the same groups ($p = 0.04$, $r = -60$). **Conclusion:** However, there was no correlation between these cellular populations in the AC group. Thus, these results suggest that although the frequencies of Th17 and Treg lymphocytes are similar between the groups, the presence of distinct patterns of association between these subpopulations as well as the detection of phenotypic changes makes it necessary to further investigate the immunoregulatory mechanisms involved in the response against the virus and the functionality of those cells.

Key words: HTLV-1; Treg cells; TH17; HAM/TSP

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ANTI-TAX LEVELS IN HTLV-1 SYMPTOMATIC AND ASYMPTOMATIC CARRIERS FROM A BRAZILIAN AND ARGENTINEAN COHORTS

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Background: The HTLV-1 (Human T-lymphotropic virus 1) induces myelopathy (HAM/TSP), adult T-cell leukemia (ATL) and other inflammatory and rheumatologic diseases. The HTLV-1 Tax protein is a regulator of gene expression, highly immunogenic being suggested in several studies that anti-Tax antibodies are involved in the pathogenesis of HAM/TSP. The aim of this study was to evaluate the anti-Tax-IgG reactivity in HTLV-1 infected individuals from a Brazilian and Argentinean cohorts and to correlate the levels of anti-Tax antibodies with clinical condition and sex. **Methods:** A total of 154 individual were enrolled from Brazilian cohort: 34 seronegative (NP-Br), 48 HTLV-1 asymptomatic carriers (AC-Br) and 47 with HAM/TSP (HT-Br); and 25 from Argentinean cohort: 10 symptomatic (Sym-Ar; 9 female and 1 male; age mean 52,1) and 15 asymptomatic (AC-Ar; 4 female and 11 male; age mean 38,9). The anti-Tax-IgG reactivity was assessed using an in house ELISA based on a prokaryotic recombinant C-terminal Tax. **Results:** The Brazilian group with HAM/TSP installed showed the greatest reactivity for the Tax recombinant protein, with the highest O.D mean, followed by the symptomatic group from Argentina (Mean O.D: HT-Br 1.335> Sym-Ar 1.091 > AC-Ar 0.824 > AC-Br 0.6742). It is interesting to highlight that the difference between mean O.D for individuals asymptomatic and symptomatic from Brazilian cohort was significant ($p<0.0001$), while these difference among individuals from Argentinean cohort was not ($p=0.5579$) and that 73.3% of the individuals asymptomatic carriers from Argentinean cohort showed reactivity to Tax (while for the Brazilian cohort this number was 36.17% and world data shown 25-60%). The asymptomatic individuals from Argentinean and Brazilian cohorts presented, respectively, 20 and 18.75% of samples showing anti-Tax O.D higher than the mean of HAM/TSP patients. In the Argentinean cohort, of the total number of reactives, 66.6% (10) were female, while 33.3% (5) were male. In the Sym-Arg group, female represented 87.5% of reactive individuals despite being a group with few samples, this tendency has been observed in other studies. **Conclusion:** Although the anti-Tax response per se is not assumed as a biomarker to predict an infected patient to be at risk to develop HAM/TSP and other neurological disorders, the asymptomatic individuals from both cohorts with high levels of antibodies seen in this study should be followed at shorter time intervals once they could be in risk for worst outcome.

Key words: HTLV-1; anti-tax; asymptomatic

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EVALUATION OF REGULATORY T-LYMPHOCYTES IN INDIVIDUALS INFECTED WITH HTLV-1

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Background: Human T-cell lymphotropic virus type 1 (HTLV-1) is the etiological agent of HTLV-1-associated myelopathy/ tropical spastic paraparesis (HAM/TSP). This virus induces an important activation of immune system leading to T-cell spontaneous proliferation and proinflammatory cytokine secretion. Regulatory T-cells (Tregs) maintain the immune system homeostasis and control the immune response. The effect of HTLV-1 infection on Tregs is still unknown. **Aim:** To investigate the profile of cytokine production of CD4+- and CD8+-Treg subsets in HTLV-1- infected individuals. **Methods:** HTLV-1-infected individuals asymptomatic (ASS) and with HAM/TSP diagnosis (ten in each group) were matched by sex and age. Non-infected individuals (NI) composed a control group. Peripheral blood mononuclear cell were cultivated for 24 hours in the presence or absence of phytohaemagglutinin stimulus prior to be labeled with monoclonal antibodies (anti-CD3, anti-CD4, anti-CD8, anti-CD25, anti-FOXP3, anti-IL-10 and anti-TGF- β). The frequency of CD4+- and CD8+-Tregs producing or not Interleukin-10 (IL-10) and/or Transforming growth factor β (TGF-β) were quantified using flow cytometry. **Results:** There were no differences in the frequencies of both CD4+- and CD8+-Treg subsets among HAM/TSP patients (CD4+: 1.6%, IQR 0.9-2.3%; CD8+: 0.7%, IQR 0.55-6.1%); ASS individuals (CD4+: 0.6%, IQR 0.24-1.5%; CD8+: 1.2% IQR 9.4- 1.2%) and NI control group (CD4+: 0.9%, IQR 0.2-1.6%; CD8+: 0.6% IQR 0.2-1.7%) (p=0,4). The frequency of CD4+-Tregs expressing only IL-10 was statistically higher in HAM/TSP group (7% IQR 6-40%) when compared to ASS (0% IQR 0-1.5%) (p=0.008) and NI (2.4% IQR 0-12.7 %). In addition, higher frequency of polyfuctional CD8+-Treg subpopulation (producing both IL-10+ and TGF-β+) was observed in HAM/TSP (25.3% IQR 3.2-66.7%) and ASS (18.3% IQR 9.8-29.6%;) groups compared to NI group (0% IQR 0-8.3%) (p=0.008 and 0.036, respectively). Interestingly, the majority of CD4 + and CD8+ Treg subsets from NI group (CD4: 68%, IQR 45-79% and TCD8: 79%, IQR 5-98%) did not produce any cytokine when compared to HAM/TSP (TCD4: 24%, IQR 16-50% and TCD8: 0%, IQR 0-14%), p=0.01. **Conclusion:** These preliminary results indicate that CD4+-and CD8+-Treg subsets from HAM/TSP individuals are activated and express higher levels of regulatory cytokines. Further studies should be conducted to better explore the role of these cells in the development of HAM/TSP.

Key words: HTLV-1; Treg cells; HAM/TSP

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EVALUATION OF IFN-γ SECRETION IN HTLV-1-INFECTED SUBJECTS USING ELISPOT

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Background: There are approximately 5-10 millions with HTLV-1 infection worldwide, and around 1-10% will result in HAM/TSP. This disabling neurodegenerative disease is mediated by inflammatory cytokines secreted by immune cells, and the IFN-γ plays as the role major in this process. Aim: This study investigated the possibility of quantification of IFN-γ secretion cells has a predictive marker for HAM/TSP development. Methods: The volunteers were selected from HTLV clinic in Institute of Infectious Diseases "Emilio Ribas" in Sao Paulo –Brazil, were invited to participate after reading and signing a consent form, and classified according their neurological status. They were classified in 4 groups: 1 – 30 cases with HAM/TSP, 2 – 30 asymptomatic HTLV-1 carriers, 3 – 9 Intermediary Syndrome (SI) and 4 – 30 health seronegatives for HTLV infection. A blood collection in heparinized tubes following a PBMC separation by gradient density fycoll-hypaque. The cell culture was done in a pre incubated EliSpot plate, the PBMC was plated in triplicate. After an incubation period of 20 hours, the plate was reading in AID EliSpot Reader (AID, GER). The statistical analysis was done with non-parametric tests (One-way ANOVA, MW, statistical column). Results : The ratio women/men was 19/11 in the controls; 24/6 for asymptomatic, 20/10 for HAM/TSP and 6/3 for SI. The age was 18-65 years old. The baseline IFN-y cell secretion occurred in majority of the HTLV-1-infected individuals, with the highest in the HAM/TSP group and SI. There was a strong correlation with SFC (Spot Forming Cells) with the clinical status ($p < 0.0001$). Conclusion: The EliSpot method can be useful to evaluate and monitor the spontaneous IFN-y FSC and possibly identify the most risk patients for the HAM/TSP. This technique could be done to monitor the inflammation level, and may be a predictive marker for disease progression.

Keywords: HTLV-1, ELISPOT, IFN-GAMMA

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FUNCTIONAL ACTIVITY OF NATURAL KILLER CELLS OF INDIVIDUALS INFECTED BY HTLV-1

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Background: High Human T-lymphotropic virus type 1 (HTLV-1) proviral load is associated with HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) development. The ability of natural killer (NK) cells to kill a variety of virus-infected cells is a sum effect of a delicate balance between the effects of inhibitory and activating NK cell receptors. **Aim:** To investigate the phenotypic profile ad the function capacities of NK cells in the context of HTLV-1 infection. **Methods:** Individuals with HAM/TSP diagnosis and HTLV-1 asymptomatic subjects (ASS) followed at the Public Health HTLV reference center of Salvador, Brazil were evaluated. Blood samples from healthy blood donors served as controls. NK-cell surface receptors (NKG2D, KIR2DL2/KIR2DL3, NKp30, NKG2A, NKp46, TIM-3, PD-1), intracellular lytic markers (Granzyme B, perforin), and functional markers (CD107a for degranulation, and IFN-γ production) assay in the presence or absence of standard K562 target cells were performed by flow cytometry. Results: NK cells from HTLV1-infected patients showed normal phenotype, whereas the frequency of NKp30 was significantly decreased in HAM/TSP patients (52%, IQR 28-61) compared to controls (73%, IQR 54-79, p=0.01). In un-stimulated state, the frequency of lytic markers (perforin, granzyme B), CD107a and IFN-γ was higher in NK cells from HAM/TSP and ASS, than controls. In contrast, after stimulation, the frequency of CD107a+ NK cells was not increased in HAM/TSP subjects, compared to other groups, consistently with a significant decreased of Granzyme-B expression. **Conclusion:** Taken together, these data suggest that NKp30 expression as well as the functional capacities of NK cells could play a key role in HTLV-1, and more especially in subjects with HAM/TSP diagnosis.

Key words: HTLV-1; NK cells; NKp30; HAM/TSP

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FREQUENCIES OF CIRCULATING TH17, TH22 AND TH1 CELLS IN PATIENTS WITH HTLV-1 ASSOCIATED MYELOPATHY/ TROPICAL SPASTIC PARAPARESIS (HAM/TSP)

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Background: T-helper (Th) 17 and Th22 cells were correlated with several inflammatory diseases. However, their roles in the pathogenesis of HTLV-1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) remains to be elucidated. This study is aimed at examining the clinical significance of circulating Th22, Th17 and Th1 cells in HAM/TSP patients and HTLV-1 asymptomatic carriers (AC). **Methods:** Twenty-five AC and 9 HAM/TSP patients were included in the study. Their peripheral blood mononuclear cells were isolated and stimulated with phytohemagglutinin (PHA) for 24h. The frequencies of circulating total Th17 (CD4+ IFN-γ- IL-17+ IL-22-), Th17 IL-22+ (CD4+ IFN-γ- IL-17+ IL-22+), Th17 IFN-γ+ (CD4+ IFN-γ+ IL-17+ IL-22-), Th22 (CD4+ IFN-γ- IL-17- IL-22+), Th22 IFN-γ+ (CD4+ IFN-γ+ IL-17- IL-22+) and Th1 (CD4+ IFN-γ+ IL-17-IL-22-) cells were determined by flow cytometry. **Results:** The peripheral frequencies of "classical" Th17 and Th22, and Th1 lymphocytes, were similar between the groups (p= 0.36, p= 0.93 and p= 0.84, respectively). Moreover, despite similar cell frequencies, correlation analyzes showed that total Th17 cells has a strong positive correlation with Th1 cells in HAM/TSP group (p= 0.01, r= 0.81). Also in symptomatic group, Th22 cells were moderately positive correlated with Th17 IL-22+ cells (p= 0.03, r= 0.69). In addition, IL-22 producing Th17 cells were weakly correlated with Th22 cells (p= 0.04, r= 0.39), and moderately positive correlated with total Th17 (p= 0.006, r= 0.53) in asymptomatic carriers group. However, there were no significant correlations between total Th17 and Th22 or Th22 IFN-γ+, Th17 IFN-γ+ and Th22 IFN-γ+, and neither among Th22 and Th1 cells in both groups. Although the frequencies of the subpopulations studied were similar between groups, the correlations found between total Th17 and Th1 cells, and Th22 with Th17 IL-22+, suggest a synergistic inflammatory response. **Conclusion:** Thus, Th17 and Th22 cells, in addition to Th1 cells, together may have a role in HAM/TSP progression. However, how Th17, Th22 cells and cytokine levels produced by them affect the disease course of HAM/TSP, or the onset of other inflammatory disorders associated with HTLV-1 requires further elucidation.

Key words: HTLV-1; HAM/TSP; TH17 cells; TH22 cells; TH1 Cells

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PLASMATIC CYTOKINE LEVELS OF CO-INFECTED PATIENTS WITH STRONGYLOIDES STERCORALIS AND HTLV-1

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Background: Strongyloides stercoralis is one of the most common human gastrointestinal parasites in the world. This parasite has the ability to replicate in the human host, permitting ongoing cycles of auto-infection that can persist for decades without further exposure to exogenous infection. S. stercoralis infection can range from asymptomatic infections to chronic strongyloidiasis. Frequently, parasite uncontrolled multiplication (hyperinfection) and potentially life-threatening dissemination of larvas occurs in immunocompromised patients and results in a high death rate (up to 85%). One of the most commonly associated conditions to severe strongyloidiasis is HTLV-1 infection. Several studies point to the immune response impaired by HLTV-1 infection may cause severe strongyloidiasis in these individuals. The objective of this study is to evaluate the plasma levels of cytokines from patients co-infected with S. stercoralis and HTLV-1. **Methods:** Plasma of twelve individuals from the same family was collected between June and October 2016. The whole family had been previously diagnosed with HTLV-1 infection and three members were identified with S. stercoralis hyperinfection. Plasma cytokines levels were measured by Cytometric Bead Array using Human Th1/Th2 cytokine kit (BD, San Jose, CA). **Results:** The levels of IL-4 and TNF-α was higher in co-infected patients (1.94 pg/mL and 1.98 pg/mL, respectively) compared to non-co-infected patients (1.82 pg/mL and 1.88 pg/mL, respectively) ($p<0.05$). Similar to other helminth infections, strongyloidiasis elicits T-helper type 2 (Th2) responses with production of IL-4 and IL-5, IgE antibodies, eosinophils and mast cells which participate in clearance of parasites. Some studies demonstrated that HTLV-1 induce the immunologic shift to T-helper type 1 (Th1) responses, reducing the Th2 response. **Conclusion:** In this study, co-infected patients presented high levels of Th2 and Th1 cytokines indicating that HTLV-1 may be interfering in protective immune response against S. stercoralis. The evaluation of specific cellular and humoral response to S. stercoralis antigens is being conducted to better understand the immune response in co-infected individuals.

Keywords: Strongyloides stercoralis; HTLV-1; immune response

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STRONGYLOIDES STERCORALIS HYPERINFECTION IN HTLV-1 INFECTED PATIENTS: A CASE REPORT

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Background: In most individuals, Strongyloides stercoralis infection remains asymptomatic. This parasite-host balance can be disrupted under conditions of impaired cellular immune response. High risk groups include patients under massive corticoid therapy, chronic alcoholics and Human T-Cell Lymphotropic Virus type 1 (HTLV-1) co-infected patients. HTLV-1 represents a significant risk factor for the development of life-threatening strongyloidiasis. Studies suggested that this may be related to HTLV-I driven decrease of T-helper type 2 (Th2) responses. The aim of this study is to describe three cases of patients co-infected with S. stercoralis and HTLV-1 presenting an uncommon clinical feature. **Methods:** Three patients, two male and one female, from the same family, between the ages from 9 to 13 years, were diagnosed with HTLV-1 infection. All of them were residents of the same house in Baia de Camamu, Bahia, Brazil, and the parents were previously diagnosed with HTLV-1. **Results:** At the parasitological examination, was observed a large amount of filariform (mean of 2,000 larvae per gram of feces) and rhabditiform larvae (mean of 2,500 larvae per gram of feces). Also, in two patients were found free-living adult female (mean of 50 parasites per gram of feces). In one of patients also was observed eggs (58 eggs per gram of feces). All patients reported intermittent diarrhea, abdominal pain and difficulty breathing. In addition, they presented skin manifestations. From May 2015 to October 2016, four points of visits were performed to obtained blood and fece samples. In the first point, only one of them was diagnosed with S. stercoralis, the other two cases were diagnosed in the third point. In the last point, three months after the last ivermectin treatment, were not found larvae in feces of any patients. The plasma of patients was obtained at each visit. The plasmatic cytokine levels were measured by Cytometric Bead Array using Human Th1/Th2 cytokine kit (BD, San Jose, CA). There was found detectable levels of cytokines IL-2, IL-4, IL-6, IL-10, TNF-α, INF-γ and IL-17 in all samples of patients. The levels of IL-17 was 19 times higher in the last point evaluated (19.2 pg/mL) compared to other points. **Conclusion:** Several authors have reported that IL-17 has a role in protecting against extracellular bacteria and fungi due to recruitment of neutrophils into the areas of infection. This is the first study that shows a significant alteration in the IL-17 levels before treatment S. stercoralis in co-infected patients with S. stercoralis and HTLV-1.

Keywords: Strongiloides stercoralis; HTLV-1; case series

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CLINICAL AND IMMUNOLOGICAL HTLV-1-ASSOCIATED FEATURES IN A FAMILY CLUSTER FROM AN ENDEMIC AREA OF BRAZILIAN AMAZON HIGHLAND

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Background: HTLV-1 infection, manifestations, clinical evolution, immunological profile and the impact of mielopathy and associated diseases in family groups still were not well clarified. Studies have reported that familiar cases tend to present the onset of the symptoms earlier than non-familiar cases and have their own features, but most researches have reported clinical and epidemiology approaches. This study aim to describe functional, clinical and immunological features of HTLV-1 carriers who belong to a family cluster. **Methods:** 17 subjects from a brazilian endemic área, in the state of Pará were included, from June 2014 to February 2016. HTLV-1 infected groups (12 subjects) were compared and separated according to family clustering (6 in each group); 5 non-infected individuals were classified as control. Clinical features were described and immunological analysis were developed through Cytoflex flow citometer (Beckman Coulter Inc., Brea, CA, EUA) to describe the expression of integrins and Treg subsets in TCD4+ and TCD8+ cells. IL-6 was analyzed through Quantikine@ELISA (R&D Systems, Minneapolis, MN, USA). **Results:** Different HTLV-1 manifestations were noticed on familiar group more than in non-familiar one, and neurological features were predominant. The expression of CD49d+ was observed in both familiar and non-familiar groups when compared to control group; expression of CD25+Foxp3IL-10+ was not significant; IL-6 was positive for both infected groups. Pro viral load had no significant differences between them. **Conclusion:** several different features found were not reported in previous studies which address family aggregation and the hipothesis of same diseases in members of a same family; our results also differentiate from a recent systematic review in other findings as more than four affected individuals where 2 of them have HAM-TSP and none developed ATL; indeed we observed that the immunological differences were related to control group, suggesting diseases in familiar clusters seem to be more an epidemiological than biological matter; furthermore social behaviour, route of transmission and environmental factors may have an important role on HTLV-1 infection and can also influence manifestations appearing as much as genetic and immunological factors can do.

Key Words: HTLV-1, Family cluster, immune response

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EVALUATION OF GRANZYME B AND PERFORIN-EXPRESSING CD8+ T-LYMPHOCYTES FROM HTLV-1-INFECTED PATIENTS WITH HAM/TSP

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Background: HTLV -1 was the first human retrovirus described and is classically associated with adult T-cell leukemia/lymphoma (ATLL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP is a chronic and progressive inflammatory disease of the central nervous system and your immunopathogenic mechanisms are not completely understood. The role of cytotoxic T-lymphocytes (CTLs) in the pathogenesis of this disease is still undefined. In this study we evaluated the cytotoxic potential of cytotoxic T-lymphocytes from HTLV-1-infected patients with HAM/TSP. **Methods:** Assays immunophenotyping by flow cytometry were conducted to assess granzyme B (GrzB) and perforin (Perf) expression in cytotoxic T-lymphocytes. We analyzed 13 uninfected subjects (controls) and 43 HTLV-1-infected patients - 18 without myelopathy (asymptomatic-ASS) and 25 with HAM/TSP. Infected patients showed an increased proportion of cytotoxic T-lymphocytes. **Results:** The proportion CD8+GrzB+ cells was four times higher in HTLV-1-infected patients (33.2%) compared to uninfected volunteers (8.4%, P=0.0009). The frequency of cells expressing perforin presented similar between groups (P=0.19). However, the percentage of CD8+ cells containing granzyme B and perforin was eight times higher in infected individuals (0.9% - 6.8%, P=0.006), suggesting an increased cytotoxic potential. The ASS and HAM/TSP groups showed similar frequencies of CD8+GrzB+ and/or Perf+ (P>0.05). No significant differences were observed in these cytotoxic mediators expression between the two infected groups studied. **Conclusion:** These preliminary findings suggest that cytotoxic potential of CD8+ T cells is not different between ASS and HAM/TSP HTLV-1-infected groups. Further studies will be conducted in an attempt to clarify these questions.

Key words: HTLV-1; granzyme B; perforin; TCD8+ Lymphocytes; HAM/TSP

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IFNG +874A/T POLYMORPHISM AMONG HTLV-1 INFECTED ASYMPTOMATIC PERSONS IS RELATED WITH A WORST PROGNOSIS AND DISEASE DEVELOPMENT

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Background: HTLV-1 infections are persistent and many times latent, but productive infections trigger different mechanisms of immunological responses in which cytokine production are important for the control of infection. The present study investigated the role of IFNG +874A/T polymorphisms among 153 HTLV-1 infected persons (33 clinically diagnosed as TSP/HAM, 22 with rheumatologic manifestations, 2 with dermatitis, 1 with uveitis and 95 asymptomatic persons). **Methods:** Genotyping and proviral load of HTLV-1 were performed using a real time PCR assay and the plasma levels of IFN-γ were measured using an enzyme immuno assay (ELISA). **Results:** Genotype frequencies were not significantly different, but the presence of allele T was higher ($p<0.0142$) among the asymptomatic persons. Plasma levels of IFN-γ were significantly higher ($p<0.0137$) among those with genotype TT. Their proviral load was also higher but showed no statistical significance. There was no difference in the plasma levels of IFN-γ among the symptomatic patients, even when they were ranked according to the disease presentation (TSP/HAM or rheumatologic manifestations). **Conclusion:** However, the difference among those asymptomatic with the allele T the difference was significantly higher ($p<0.0016$) and similar to the plasma levels observed among the symptomatic persons. The results suggest that the polymorphism of IFNG +874A/T may modulate the plasma levels of IFN-γ during HTLV-1 infection. Asymptomatic carriers of the polymorphic genotypes seem to develop the inflammatory response in a shorter time triggering the process of HTLV-1 related diseases. It seems to be reasonable to suggest that these persons are possible candidates to follow closer in order to foresee the upsurge of clinical disease and start available treatment procedures.

Key words: HTLV-1; polymorphism; asymptomatic

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THE INVOLVEMENT OF CHEMOKINES AND ADHESION MOLECULES IN HTLV-1 INFECTION

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Background: The human T cell lymphotropic virus type 1 (HTLV-1) infection is characterized by an exaggerated immune response with spontaneous production of TNF and IFN-γ. These cytokines increase the expression of chemokines and adhesion molecules and facilitate the entry of activated lymphocytes into CNS. The aims of this study were to evaluate the role of chemokines and adhesion molecules in the pathogenesis of HTLV-1 infection and analyze the frequency and the median fluorescence intensity (MFI) of CD4+, CD8+ and CD14+ expressing CD11a, CD49d and CXCR3. **Methods:** CXCL9 and CXCL10 and soluble ICAM-1 and VCAM-1 were assayed by ELISA in serum and cerebral spinal fluid (CSF) of HTLV-1 carrier, HTLV-1 infected individuals with manifestation of overactive bladder (HTLV-OAB) and HAM/TSP. **Results:** The levels of CXCL9 in serum of HAM/TSP (median 2428pg/ml) were significantly higher than in HTLV-OAB (1104pg/ml) and carriers (1224pg/ml), p=0,0005. CXCL10 in serum of HAM/TSP (639pg/ml) were higher than in carriers (239pg/ml) and HTLV-OAB (226pg/ml), p<0,0001. The levels of CXCL9 (1167 versus 19 pg/ml, p<0,0001) and CXCL10 (1491 versus 300pg/ml, p<0,01) in CSF of HAM/TSP were significantly higher than in CSF of HTLV-OAB. There was no difference between the levels of sICAM-1 and sVCAM-1 in serum and CSF of carrier, HTLV-OAB and HAM/TSP, p>0,005. Frequency and MFI of lymphocytes and monocytes expressing CD11a, CD49d and CXCR3 were analyzed by flow cytometry. CD4+ and CD8+ expressing CD11a was lower in HAM/TSP (29 and 65 MFI, respectively) when compared to carrier (80 and 108 MFI, respectively), p=0,01. CD14+ expressing CD11a was also lower in HAM/TSP (169 MFI) when compared to carrier (446 MFI), p=0,03. There was no difference in the expression of CD49d when the groups were compared (p>0,05). The frequency of CXCR3 on CD4+ and CD8+ was lower in HAM/TSP (11% and 47%, p=0,02) than in HTLV-OAB (34% and 77%, p=0,05). There was no difference in the expression of CXCR3 on CD14+ when the groups were compared. **Conclusion:** These findings confirm the involvement of chemokines in the migration of HTLV-1 infected cells to CNS, but are not sufficient to prove the involvement of adhesion molecules in the pathogenesis of HTLV-1. The low expression of CD11a and CXCR3 by CD4+, CD8+ and CD14+ cells of HAM/TSP patients may be related to chemoattraction of infected cells to CNS and consequent development of a chronic inflammatory disease.

Key words: HTLV-1; chemokines; adhesion molecules

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PREVALENCE OF POSITIVE TUBERCULIN SKIN TEST IN HTLV-1 INFECTED SUBJECTS AND RELATIONSHIP WITH IFN-γ PRODUCTION IN CULTURES STIMULATED WITH PPD

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Background: The association between tuberculosis (TB) and human T-lymphotropic virus type 1 (HTLV-1) has been well documented. Previous studies have reported that HTLV-1 infected subjects have impairment in the response to the tuberculin skin test (TST) as well as a decreased lymphocyte proliferative response to mycobacterial antigens. However, more recently we have shown that the TST is positive in a large percentage of HTLV-1 infected subjects. Additionally, the T cell activation in cultures without stimulus makes it difficult to drawn conclusions about the in vitro T cell response in some patients. Our hypothesis is that there is discordance between in vivo and in vitro tests to evaluate cell mediate immune response in HTLV-1 infected individuals. The aim of this study was to evaluate the positivity of the TST and the production of IFN-γ in HTLV-1 infected subjects with and without evidence of exposure to Mycobacterium tuberculosis. **Methods:** In a cross-sectional study, we evaluated the prevalence of positive tuberculin skin test (TST) among HTLV-1 infected subjects (n=162) and seronegative controls (n=162) from the Complexo Hospitalar Universitário Professor Edgard Santos, Federal University of Bahia, Brazil. To evaluate the relationship between TST positivity and in vitro IFN-γ production, peripheral blood mononuclear cells from HTLV-1 infected individuals with TST negative (n=79) or TST positive (n=101) were stimulated with purified protein derivative (PPD) and IFN-γ levels were measured by ELISA. **Results:** The overall positivity of TST was higher in the HTLV-1 infected subjects (53,7%) than in seronegative controls (34,6%), P<0.001. There was no difference in the IFN-γ production in PPD stimulated cells compared to non-stimulated cells from HTLV-1 infected individuals with negative TST (1,197 pg/ml in stimulated cells x 1,318 pg/ml in non-stimulated cells, p>0.05) or positive TST (936 pg/ml in stimulated cells x 846 pg/ml in non-stimulated cells, p>0.05). Considering the ratio of IFN-γ production by PPD stimulated/non-stimulated cells higher than 1 as a positive IFN-γ response, only 41,6% of the TST positive individuals presented IFN-γ positive response, and 31,6% of the TST negative individuals presented IFN-γ positive response. **Conclusion:** These results indicate that there is a high prevalence of M. tuberculosis infection in HTLV-1 infected subjects and there is a dissociation between TST and IFN-γ production in cultures stimulated wit PPD.

Key words: HTLV-1; tuberculin skin test; IFN-g; PPD

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EVALUATION CD4+FOXP3+ T CELL IL-10 AND TGF-γ PRODUCERS IN KERATOCONJUNCTIVITIS SICCA ASSOCIATED WITH HTLV-1

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Background: HTLV-1 is the causative agent of leukemia/lymphoma adult T-cell (ATLL), tropical spastic paraparesis / myelopathy associated with HTLV-1 (HAM / TSP) and uveitis. In addition, keratoconjunctivitis sicca (KCS), a multifactorial disease of the tear and of the ocular surface, has beenmore frequently reported in patients infected with HTLV-1. As for other HTLV-1-associated diseases, KCS has been related to a high proviral load. Regulatory T (Treg) cells are important in maintaining the homeostasis of the immune system. An impairment in theimmunoregulation function of Treg may contribute to the inflammatory environment observed in the KCS. This study aimed to evaluate the Treg cells of patients with KCSassociated with HTLV-1. **Methods:** Assays immunophenotyping by flow cytometry were conducted to assess the frequency of CD4+Treg cells(FOXP3+), as well as IL-10 and TGF-β productionby Treg. Thirty-sevenHTLV-1 individuals wereincluded (27 asymptomatic for HAM/TSPwith positive diagnosis of ocular manifestation (KCS),10 with negative diagnosis (ASS -asymptomatic). Seventeen non-infected individuals were included as controls (NI). **Results:** The frequencies of CD4+FOXP3+T cells were significantly higher in KCSand ASS groups when compared to non-infected individuals. As the production of immunosuppressive cytokines, a higher frequency of CD4+FOXP3+double producers of IL-10 and TGF-β in the KCSgroup was observed when compared to group ASS. **Conclusion:** Our results suggest that while occurs an expansion of Treg cells in HTLV-1, there isnotanefficiently controlofcell activation. Future studies should be conducted to assess more accurately the regulatory mechanisms played by Treg CD4+.

Key words: HTLV-1; Keratoconjunctivitis sicca; Treg cell; Foxp3+; IL-10; TGF-B

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ESTIMATION OF HTLV-1 VERTICAL TRANSMISSION CASES IN BRAZIL PER ANNUM

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Background: Brazil presents the highest absolute number of HTLV infected individuals in the world. This virus can be transmitted via sexual intercourse, contact with blood and from mother to child, mainly by breastfeeding. Treatments for the high morbidity/mortality associated diseases (ATL and HAM/TSP) are limited. Therefore, infection prevention is of utmost importance. However, antenatal screening is not routinely performed in Brazil. Lack of data regarding the number of individuals infected via breastfeeding impairs the development/implementation of government policies. In 2014, for example, there were 72 new diagnoses of HIV infection reported in children under 5 years. However, this number is not known for HTLV infection. Our aim is to estimate the number of HTLV infections that occurs annually due to mother to child transmission (MTCT) in Brazil. **Methods:** For the estimation of the number of HTLV-1 cases due to MTCT per year in Brazil, the following variables were used: number of births in Brazil, prevalence of HTLV-1 infection in pregnant women in the country, breastfeeding duration rate, transmission risk according to breastfeeding period. We also estimated the number of HAM/TSP and ATL cases due to MTCT according to the risk of each disease onset. **Results:** In 2014, there were 2,979,259 births in Brazil. Considering HTLV-1 prevalence in pregnant women in Brazil (0.1-1.05%), it is estimated that there are 2,929–30,757 infected pregnant women/year. 84.6% and 77.6% of women are breastfeeding at 4 and 6 months after childbirth. Extrapolating this data and considering 3.9% and 20.3% the risk of HTLV transmission before and after 6 months period of breastfeeding we estimate that there are 469-4,929 new cases of HTLV-1 infection due to MTCT annually in Brazil. Moreover, it is known that 2.5% of infected women transmit HTLV-1 regardless of breastfeeding. Therefore, 73-769 new vertical infections should occur annually and could not be avoided by the use of breast milk substitutes. Considering 4% and 1% the risk of ATL and HAM/TSP development 18-197 ATL and 4-49 HAM/TSP cases should occur in the future due to MTCT. **Conclusion:** The study showed a high number of new HTLV-1 infections due to MTCT every year in Brazil. When comparing to other diseases that are currently tested in antenatal or neonatal screening, such as HIV, the result is more evident. The antenatal screening and avoiding breastfeeding is essential to reduce the HTLV neonatal infection. More studies regarding the cost/effectiveness of antenatal screening may be helpful.

Key words: HTLV-1; vertical transmission; estimation

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ESTABLISHMENT OF A REPORTER CELL LINE EXPRESSING HTLV-1 TAX FOR ANTIVIRAL SCREENING ASSAYS

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Background: Human T cell lymphotropic virus type 1 (HTLV-1) causes two main diseases: HTLV-1 associated myelopathy/ tropical spastic paraparesis-HAM/TSP, and adult T cell leukemia/lymphoma-ATL. Currently, there is no cure and no vaccine for this infection, and therapeutic approaches have variable effectiveness. Thus, it is important to identify efficient antiviral compounds. Some studies have adopted reporter cell lines based on green fluorescent protein (GFP) expression under the control of viral promoter region, since these tools are fast, easy and inexpensive for antiviral drug studies Aim. To construct and characterize a reporter cell line, which carries GFP gene under the control of the long terminal repeat (LTR) promoter and an inducible tax gene for a future antiviral screening assay. **Methods:** Jurkat LTR-GFP cell line was co-transduced with lentiviral particles (pLVX-Tet3G [G418] + pLVX-Tet3G itax [Blasticidin]), or just with pLVX-Tet3G [G418]) at a multiplicity of infection 1:10 in order to generate a reporter cell line based on inducible gene expression system – Tet-On®, in which doxycycline can promote the tax expression. After 24h, cells were cultivated in cell culture medium containing G418 and blasticidin for selection of transduced cells. Later, the characterization of Jurkat LTR-GFP inducible-tax was performed. For that, these cells were incubated with different concentrations of doxycycline (0.01 – 1 µg/ml) for tax induction. After 48h and 72h, the GFP expression was assessed by flow cytometry and fluorescence microscopy. Jurkat LTR-GFP inducible-tax without doxycycline and Jurkat LTR-GFP Tet3G were used as controls. Moreover, tax expression was evaluated by flow cytometry, in which MT-2 cell line was adopted as positive control. **Results:** Jurkat LTR-GFP inducible-tax cell line expressed GFP after incubation with different concentrations of doxycycline for 48 and 72h, respectively: 10.1% and 11.4% (0.01 µg/ml), 15.3% and 19.7% (0.1 µg/ml), and 19.3 % and 22.6% (1 µg/ml). Thus, incubation with 1 µg/ml of doxycycline during 72h was a suitable condition for the assays. Jurkat LTR-GFP Tet3G with and without doxycycline did not express GFP significantly as well as Jurkat LTR-GFP inducible-tax without this inducer. Moreover, 43.1% of Jurkat LTR-GFP inducible-tax (GFP+) expressed Tax after induction with doxycycline similarly MT-2 cell line (65%). **Conclusion:** Cellular transduction with lentivirus combined with doxycycline-inducible expression systems was an efficient strategy for Tax expression on Jurkat LTR-GFP cells. In addition, the establishment of this reporter cell line is a powerful tool for drug screening assays in order to identify antiviral compounds that inhibit HTLV-1 Tax expression and/or LTR transactivation.

Key words: HTLV-1; tax; screening assays

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POTENTIAL OF A CHIMERIC MULTIEPITOPE PROTEIN LVBA-RECHTLV-1/2 AS ANTIGEN FOR THE DEVELOPMENT OF A NEW DIAGNOSTIC TOOL

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Background: The Human T-lymphotropic virus (HTLV) is the first retrovirus isolated in humans. HTLV-1 is responsible for causing Adult T-cell leukemia/lymphoma (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and other important inflammatory conditions. Clinical manifestations with HTLV-2 are not very common, although there are some reports of a similar HAM/TSP syndrome and association with bacterial infections. According to the algorithm suggested by the Ministry of Health, the serological diagnosis is based on the detection of specific antibodies against HTLV-1/2. However, the occurrence of indeterminate results indicates the need to improve the currently tests. Also, the development of alternatives and national inputs technology for screening of blood products is essential to ensure the implementation and maintenance as health procedure with full coverage by the state and also to be transferred to Brazilian blood banks after validation. The multiepitope proteins are a new approach in the development of tests for various infectious agents, with high sensitivity and specificity, resulting from increased epitope density. The aim of this work was to construct a chimeric protein (LVBA-recHTLV-1/2) with immunodominant antigens for HTLV-1 and HTLV-2 for the development of screening and confirmatory tests for HTLV-1/2 infections. **Methods:** LVBA-recHTLV-1/2 was designed using p19, gp46 and Tax sequences of HTLV-1 and 2 and a histidine tail for protein purification in Äkta Start system by histidine affinity chromatrography columns after expression in Escherichia coli Rosetta-gami2(DE3). Western blot assay using pool of sera from HTLV-1+ or HTLV-2+ individuals and serum from uninfected individuals (GIPH cohort) were performed after purification. An indirect ELISA in house was developed using the chimera in the solid phase and HTLV-1+, HTLV-2+ and seronegative sera from the GIPH cohort and from a cohort containing subjects from São Paulo and Pará was performed to test specificity and sensibility. **Results:** In Western blot assays the chimera was able to recognize in a specific manner pool of sera from HTLV-1+, HTLV-2+ (GIPH cohort) and commercial anti-histidine monoclonal antibody, but not the uninfected individuals pool of sera (GIPH cohort). Using an indirect in house ELISA, the LVBA-recHTLV-1/2 was able to specifically differentiate sera from HTLV-1+ and HTLV-2+ individuals and seronegative individuals (GIPH, São Paulo and Pará cohort) with significant statistical difference ($p < 0.0001$). The ROC curve analysis showed great accuracy with area under the curve of 0.9787. **Conclusion:** It was concluded that the chimera possesses great potential as antigen for the development of assays for HTLV-1/2 screening and confirmatory diagnostic.

Key words: HTLV-1; chimeric protein; diagnostic

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IMPROVEMENT IN THE SEROLOGICAL DIAGNOSIS OF HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1 AND 2

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Background: Considering the absence of systematic evaluation of the serological diagnostic kits for HTLV infection currently available in Brazil, the fourth country with the highest prevalence of this infection in the world, this study aims to evaluate the performance of serological diagnostic tests for screening and confirmatory for HTLV antibodies, which are commercially available in Brazil, to improve the serological diagnosis of HTLV-1/2 infection. **Methods:** For this, an accuracy study of the Murex HTLV-1/2, Symbiosys HTLV-1/2 and Gold Elisa HTLV-1/2 branded screening tests was performed, Using 208 samples from individuals infected with HTLV and 201 samples from non-infected individuals, and performance evaluation of commercially available Western Blot 2.4 genelab serological confirmatory tests by testing the 208 positive samples and the INNO-LIA® HTLV-I / II assay, using 47 samples that were undetermined and 10 samples that presented negative serology in the confirmatory test WB2.4. **Results:** Thus, it was possible to observe that among the serological screening tests, the Murex brand test had the highest number of false positive results (16), With 99.52% sensitivity and 92.04% specificity, the Symbiosys test had the highest number of false negatives (2), with 99.04% sensitivity and 99.0% specificity, and the Gold test showed 100% sensitivity and 99.0% specificity. From the confirmatory commercial assays for serology of HTLV infection, It was possible to observe that the INNO-LIA test solved 75% of the undetermined results in WB2.4, being 19 HTLV untyped, 17 infected with HTLV-1, 02 infected with HTLV-2, 02 Negatives for HTLV infection and 07 samples continued with undetermined serology. In addition, a sample of the ten negatives in WB2.4 showed INNO-LIA reactivity. **Conclusion:** It is possible to conclude that the INNO-LIA confirmatory test is the most appropriate for the diagnosis of HTLV infection.

Key words: HTLV-1; HTLV-2; serological; diagnosis

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COMPARISON OF PROVIRAL LOAD IN PERIPHERAL BLOOD MONONUCLEAR CELLS AND VAGINAL FLUID IN HTLV-1-INFECTED WOMEN

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Background: The HTLV-1 proviral load (PVL) has been identified as an important marker of the development of HTLV-1 associated diseases. Few studies have evaluated the proviral load in compartments other than peripheral blood. This study aimed to evaluate the impact of proviral load on the vaginal ecosystem in HTLV-1 infected women. **Methods:** HTLV-1 infected women were enrolled at the HTLV Center and EBMSP gynecology clinic in Salvador. All volunteers underwent gynecological examination to collect cervical-vaginal material. Proviral load in peripheral blood mononuclear cells (PBMC) and vaginal fluid were measured by real-time quantitative Polymerase Chain Reaction (PCR), and cervical-vaginal cytopathology was evaluated using light microscopy. Quantification of cytokines in vaginal fluid was performed using the Cytometric Bead Array (CBA) Human Th1 / Th2 / Th17 kit. The association between PVL in PBMC and vaginal fluid was assessed by Pearson's correlation. **Results:** 48 infected women were evaluated. Vaginal PVL was detectable in 27 (56.25%) women and undetectable in 21 (43.75%), of whom 3 had equally undetectable PVL in peripheral blood. The PVL was statistically higher in the blood, with a median of 23,260 copies / 106 PBMC (IQR: 3,858 - 68,690) and a median of 200 copies / 106 cells in vaginal fluid (IQR: 0 - 2,672) ($p<0.001$). There was a positive correlation between PVL in peripheral blood and vaginal PVL ($p<0.001$). When evaluating cytokine levels in vaginal fluid, it was observed that IL-10 levels in women with undetectable vaginal PVL were statistically higher than those with detectable vaginal PVL. No differences were observed in the levels of IL-2, IL-4, IL-6, IL-17, TNF and IFN-γ in the vaginal fluid between the groups with detectable or undetectable vaginal PVL. Regarding PVL in PBMC, cytokine levels in vaginal fluid of women with detectable PVL were similar to those in women with undetectable PVL. **Conclusion:** There was a direct correlation between PVL in peripheral blood and vaginal PVL. A regulatory cytokine increase in vaginal fluid was observed in women with undetectable vaginal PVL. Studies should be conducted to better evaluate this association.

Key words: HTLV-1; proviral load; PBMC; vaginal fluid

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META ANALYSIS OF HTLV EXPRESSION INFLUENCE: A ROBUST BIOINFORMATIC APPROACH

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Background: Human T-cell Lymphotropic Virus (HTLV) is a neglected sexual transmitted disease that causes at most of times asymptomatic disease. **Methods:** Meta analysis was performed assessing the NCBI GEO data bank and datasets were downloaded by GEOQuery. The datasets were normalized, collapsed using WGCNA, merged and batch effect removed by ComBat. The datasets were grouped based on type of cell (CD4, PBMCs and miRNA) and analysed separately. The Differential Expressed Genes (DEGs) were be calculated by limma. **Results:** In total, 36 datasets were retrieved and 28 datasets were excluded from analysis due methodology incompatibility. A total of 8 datasets were eligible, 2 from CD4+ cells infected, 4 from peripheral mononuclear cells (PBMCs) and 2 analysis of miRNA with total of 77 controls samples, 110 Adult T-Cell Leukemia/Lymphoma samples (ATL), 36 HTLV-1 associated myelopathy/tropical spastic paraparesis samples (HAM/TSP) and 47 asymptomatic samples. The normalization were done and the batch effect removed and a total of 10269 genes of PBMCs, 13276 of CD4 and 790 miRNAs were identified. The differentially expressed genes (DEGs) were assessed using an absolute log2-fold-change threshold of ≥1.0, and multiple t-tests comparisons were performed using the false discovery rate (FDR) set at 5%. We found 733 differentially expressed genes in the ATL vs Control. Three genes were differentially expressed in the HAM/TSP vs Control and no differential expression were observed when compare the asymptomatic to Control. **Conclusions:** This study is the first steps of the bioinformatic analysis of public datasets disponible in GEO and it can brings great advance in development of a vaccine or treatment for HTLV carriers. Moreover, future analysis using machine learning approach will be performed to refine this gene set and identify possible biomarkers and identify the associated pathway for laboratory confir.

Key words: HTLV-1; expression; bioinformatic

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PREVALENCE OF MUTATIONS ASSOCIATED WITH ATL IN A POPULATION FROM SALVADOR, BAHIA, BRAZIL

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Background: Adult T cell leukemia/lymphoma (ATL) is a malignant T cell neoplasm associated with Human T Cell LeukemiaVirus Type-1 (HTLV-1) infection, whose pathogenesis and genetics basis are poorly understood. ATL originates from T cells infected by HTLV-1 in early infancy, predominantly in individuals who acquired the virus infection as a result of breast feeding, with ATL evolving after a long latency period of >30-50 years. ATL pathogenesis is developed in 3-5% of HTLV-1 infected individuals and its oncogenic mechanisms have been associated with somatic mutations in T cell receptor (TCR) -nuclear factor (NF) –kB signalingpathway, which is activated by the viral protein, Tax. In a previous study performed in ATL samples from Japan, more than 90% of ATL cases had lesions that were strongly associated with the components of TCR-NFkB signaling and the most frequently mutated genes were PLCG1andPRKCB.Once the outcome of HTLV-1 infection can be related to viral and/or host factors and there are few studies focused on the association of somatic variations and ATL development, the objective of this study is to determinate the genotypic frequencies of mutations in PLCG1 andPRKCB genes in Brazilian population. **Methods:** 1309 samples from HTLV-1 non-infected individuals from Salvador, Bahia, Brazil, included in the Social Changes, Asthma and Allergy in Latin America (SCAALA) project were genotyped using the Illumina HumanOmni2.5-8v1 bead Chip plataform. After that, quality control analysis of the data was performed. The SCAALA project compounds the EPIGEN Brazil Initiative, the most comprehensive up-to-date genomic analysis of a Latin-American population, that genotyped nearly 2.2 million SNPs, including SNPs in PLCG1 and PRKCB genes. 200 Samples from HTLV-1 infected individuals were randomly selected from the HTLV Center (Escola Bahiana de Medicina e Saúde Pública). **Results:** The partial results showed in this study comprehend the genotyping of 1309 samples (707 males and 602 females) from HTLV-1 non-infected individuals. It was observed 43 and 357 SNPs in PLCG1 and PRKCB genes, respectively. The most important variations associated with ATL development (p.Glu1163Lys and p.Asp.1165His from PLCG1 gene and Asp427 and Asp630 from PRKCB gene) were not observed in HTLV-1 non-infected individuals. **Conclusion:** The two genes analyzed were considered highly heterogeneous and none of the SNPs observed in the HTLV-1 non-infected group was previously associated with ATL development in HTLV-1 infected individuals. Further studies are necessary to confirm the prevalence of these SNPs in HTLV-1 infected individuals.

Key words: HTLV-1; mutations; ATLL; prevalence

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STING GENE POLYMORPHISMS ARE NOT ASSOCIATED WITH THE SUSCEPTIBILITY OR THE PROGRESSION TO HAM/TSP IN HTLV-1 PATIENTS

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Background: The stimulator of interferon genes (STING; encoded by TMEM173) is involved in the innate immune response and is required for host protection against a number of RNA-related pathogens, including the human T-cell lymphotropic virus type 1 (HTLV-1). STING is a signaling molecule that plays a key role in the transcription of host innate defense genes, including type 1 interferons (IFNs) and pro-inflammatory cytokines. Some studies have indicated that the presence of polymorphisms in the human STING may have an impact on innate immune signaling and affect the susceptibility to infection for a pathogen and contribute to severe inflammatory disorders such as HTLV-1 Associated Myelopathy/Tropical SpasticParaparesis (HAM/TSP). The aim of this work was to analyze STING gene polymorphisms in the development of HAM/TSP in symptomatic and asymptomatic individuals with HTLV-1. **Methods:** The polymorphisms, rs78233829, rs1131769 and rs7380824, located in exons 6 and 7, were detected by conventional PCR and subsequent sequencing. The information concerning the proviral load, TCD4 + and TCD8 + lymphocyte count and serum pro-inflammatory cytokine profile (TNF-α, TNF-β, IFN-γ and IL-6, IL-8, IL-10) were obtained from the database of the Laboratory of Virology. **Results:** The results showed that there was no statistically significant difference between the genotypic frequencies when compared to the groups of healthy controls and HTLV-1 carriers or when comparing the asymptomatic and symptomatic groups for HAM/TSS. No association was observed between the polymorphisms in the STING gene and the viral load parameters, TCD4 + / TCD8 + lymphocyte counts, and pro- and anti-inflammatory cytokines profile in patients with HTLV-1. **Conclusion:** Thus, in the present study, we conclude that no evidence was found that the polymorphisms rs78233829, rs1131769 and rs7380824 of the STING gene contribute in some way to the progression of the infection to HAM/TSP or susceptibility to HTLV-1.

Key words: STING, HTLV-1, PET/MAH

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NESTED CONTROL CASE STUDY OF HTLV-1 INFECTED INDIVIDUALS BY 18-F FDG PET/CT

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Background: Autopsy studies have demonstrated that HTLV-1 affects the central nervous system (CNS) of individuals with HAM/TSP in all its extension, but with a greater involvement of the thoracic spinal cord. The pathogenesis of the neurological diseases associated with this infection and the fact that the thoracic spinal cord is the segment most affected by HTLV-1 are not fully understood. In an attempt to clarify these doubts we developed this study with 18-F FDG PET/CT, an examination with high sensitivity to assess CNS metabolism and functional activity. **Methods:** Nested control-case study of individuals infected by HTLV-1: asymptomatic-AG (N = 21), symptomatic-SG (N = 11), HAM/TSP-HG (N = 16) and control group-CG (N = 30). All individuals infected by HTLV-1 had the infection confirmed by westen blot or PCR, 4 years or more of schooling, negative serology for coinfections (HIV, syphilis, B hepatitis, C Hepatitis, Chagas disease) and absence of other neurological comorbidities. All study participants agreed and signed a free and informed consent term. The control group consisted of individuals who participated in other studies and consented through the consent term to use their results. **Results:** 18-F FDG PET-CT standartized uptake value (SUV) from the thoracic and cervical spinal cord were lower in HTLV-1 infected individuals, with statistically significant difference, $p < 0.001$ and $p = 0.003$, respectively. This result evidenced a hypometabolism associated with infection. Thoracic spinal cord SUV had a statistically significant difference between CG and all HTLV-1 infected groups: AG, $p = 0.043$ (CI 95% 0.005-0.415); SG, $p < 0.001$ (95% CI 0.232-0.740); and HG, $p < 0.001$ (CI 95% 0.273-0.719). Thoracic spinal cord SUV value smaller or equal to 1.15 was accurate in discriminating between infected and control groups: HG and CG (94.4%, $p < 0.001$; CI 95% 0.89-1.00), HG and AG (85.7%, $p = 0.001$; CI 95% 0.72-0.97) and HTLV-1 infected and CG (81.6, $p < 0.001$ CI 95% 0.72-0.91) by ROC curve. Thoracic spinal cord SUV correlated with the degree of neurological impairment measured by the Expanded Disability Scale (EDSS) score: $rs = -.526$, $R2 = 0.28$, $p < .001$. **Conclusion:** The spinal cord hypometabolism observed in the HTLV-1 infected individuals demonstrates: neurological involvement in the majority of infected, including subclinical CNS involvement in asymptomatic patients; CNS involvement beyond the thoracic spinal cord segment; pathogenic mechanism of HTLV-1 in the CNS other than inflammatory, possibly microvascular

Key words: HTLV-1; PET/CT; 18-FFDG

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18-F FDG PET/CT OF THE THORACIC SPINAL CORD, PLASMA AND CEREBROSPINAL FLUID CYTOKINES, CHEMOKINES AND PROVIRAL LOAD AS INDEPENDENT AND MULTIVARIATE MODEL PREDICTORS OF HAM/TSP

Romanelli LCF[1,2], Miranda DM[1,4], Carneiro-Proietti ABF[2], Mamede M[1], Mendes HM[1], Martins ML[2], Ferreira ASD[2], Valadão D[1], Farias RCV[1],Pereira NC[1], Paula JJ[1], Schütze M[1],Vertchenko SB[2], Nicolato R[1,3]

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Background: The classic neurological disease associated with HTLV-1 infection is HTLV-1 associated myelopathy (HAM/TSP). In these 30 years since virus isolation, many risk factors have been associated with central nervous system (CNS) impairment. However, there are no biomarkers and complementary tests that allow an early diagnosis of CNS disease. **Methods:** Cross-sectional and nested case-control study that used 18-F FDG PET/CT, plasma and cerebrospinal fluid cytokines, chemokines and proviral load from HTLV-1 infected individuals: asymptomatic-AG (N = 21) and HAM/TSP-HG (N = 16). All individuals infected by HTLV-1 had the infection confirmed by westen blot or PCR, 4 years or more of schooling, negative serology for coinfections (HIV, syphilis, B hepatitis, C Hepatitis, Chagas disease) and absence of other neurological comorbidities. All study participants agreed and signed a free and informed consent term. 18-F FDG PET/CT of the whole body was performed and a special protocol was used to evaluate the thoracic spinal cord. Immunobead assay Milliplex MAP, a human high sensitivity T cell assay (EMD Millipore), was used to quantify expression levels of 19 cytokines in plasma and CSF. The HSTCMAG-28SK kit was designed to detect the following analytes: ITAC, GM-CSF, Fractalkine, IFN-gamma, TNF-α, MIP-3α, IL-1b, IL-12, IL-13, IL-17A, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-21, in a 96-well plate, according to the manufacturer's instructions. Plates were read using a Luminex100/200 system. Quantification of proviral load was performed by real-time PCR, using the SYBR Green method. **Results:** Univariate analysis indicated that female gender, thoracic spinal cord SUV, blood proviral load, plasma IL-6, CSF ITAC, INF-gamma and IL-8 were predictors to HAM/TSP, when they were taken as independent risk factors. Only thoracic spinal cord SUV ($p = 0.001$) and CSF ITAC ($p = 0.006$) adhered to the multivariate model, with a correct classification between asymptomatic and HAM/TSP individuals equivalent to 81.3%, constant $p = 0.048$ and adjusted $R2 = 0.65$. The increase in thoracic spinal cord SUV value was protective and of CSF ITAC was at risk for HAM/TSP. **Conclusion:** This association between thoracic spinal cord SUV and CSF ITAC in the prediction of HAM/TSP leads us to consider the possibility of a microangiopathic process evidenced by hypometabolism observed in the thoracic spinal cord in association with immunomediated process represented by CSF ITAC, chemokine with chemotactic properties on T cells, as risk factors that are associated in the HAM/TSP pathogenesis

Key words: HTLV-1; HAM/TSP; PET-CD; FDG; spinal cord; cerebrospinal fluid

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HTLV-1 ORF-I GENETIC DIVERSITY AMONG PATIENTS WITH DIFFERENT CLINICAL PROFILES

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Background: The HTLV-1 pX genome region contains four open reading frames (ORFs) that encode specific regulatory proteins. Orf-I encodes a 12 KDa protein (p12) susceptible to two enzymatic cleavages. The first cleavage results in the loss of endoplasmic reticulum retention signal while the second cleavage releases the p8 protein that moves to the infected cell surface. A recent study demonstrated that equivalent amounts of p12 and p8 proteins contributes to HTLV-1 infectivity and persistence in a macaque model. Moreover, the presence of both proteins is essential for the infected cells to escape from CTL-mediated lysis It has been showed that some natural ORF-I mutations alter p12 protein cleavage, which in turn may affect HTLV-1 proviral loads and HAM/TSP outcome. Due to the importance of both proteins to HTLV-1 infection, this study aimed to evaluate ORF-I genetic diversity and to identify natural mutations among HTLV-1-infected patients with HTLV-Associated myelopathy/Tropical Spastic Paraparesis (HAM/TSP), Adult T Cell leukemia/Lymphoma (ATL), and HTLV-Associated Infective Dermatitis (IDH). **Methods:** To characterize the Orf-I sequences, DNA samples of HAM/TSP (n=17), ATL (n=13), IDH (n=12), and 23 Asymptomatic HTLV-1 carriers (AHC) were submitted to PCR for complete Orf-I amplification and sequencing. **Results:** Analysis using Geneious R6 software revealed that the overall diversity among sequences was 0.007, confirming the low diversity of HTLV-1 Orf-I region among patients and asymptomatic individuals. Interestingly, six natural amino acid changes with frequency over 5% were identified: G29S, F61L, and S63P at transmembrane domains; P34L and S91P at SH3 binding domains, and F78L. Among these mutations, only P34L frequency was found higher within HAM/TSP group when compared to HID patients (p=0.047). In addition, despite being in low frequency, 13 mutations were observed in specific clinical profiles. The amino acid changes G25S, C39Y, F54L, P86S, and A89T were found in HAM/TSP patients, while L55F and F84L mutations were identified in IDH and ATL patients, respectively. **Conclusion:** The relatively low sample size makes further investigation necessary in order to determine whether these mutations are particularly present in specific patient groups. Importantly, most mutations found in the present study are located in functional motifs of ORF-I region, which may impact in the localization and function of these regulatory proteins. Finally, the important role of p12 and p8 proteins in HTLV-1 infection and their low genetic diversity found here suggest that this region could be used in HTLV-1 therapeutic approaches.

Key words: HTLV-1; ORF-I; genetic diversity

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PRODUCTION OF RECOMBINANT PROTEIN OF HTLV-1 TAX, HBZ AND HBZ-SI

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Background: Human T-lymphotropic virus type 1 (HTLV-1) infects and induces polyclonal expansion of T CD4+ lymphocytes. HTLV-1 TAX protein promotes replication of provirus as well lymphocyte activation, proliferation, survival and transformation of the infected cells. TAX is an important antigen once it triggers specific CD8+T lymphocytes to induce apoptosis of infected cells. HTLV-1 HBZ and/or HBZ-SI proteins may promote proliferation and immortalization of infected cells. Thus, to inhibitthese proteins might reduce the progression of the virus and prevents the development and associated diseases. Aim: To produce the HTLV-1 proteins TAX, HBZ and HBZ-SI and select drugs capable of inhibiting their activity, that could be useful in the treatment of individuals infected HTLV-1. **Methods:** DNA constructions encoding a peptide leader sequence and TAX, HBZ and HBZ-SI and His-Tag optimized for expression into insect cells were synthetized by GenScript and subcloned into pFastBac1 plasmid. Recombinant baculovirus constructions obtained from Sf9 cells were used to determine de best conditions to produce recombinant proteins in the supernatant of High-five cells. **Results:** Recombinant baculovirus constructions encoding TAX, HBZ and HBZ-SI were successfully generated. The best multiplicity of infection (MOI) and time of infection (TOI) for recombinant protein production were determined as MOI 10 and TOI 72 h. Recombinant TAX showed doublet band with 45 kDa in Western blot assay. **Conclusion:** Secreted HTLV-1recombinant tax was successfully produced inbaculovirus insect-cell system.

Key words: HTLV-1; recombinant protein; TAX; HBZ; HBZ-SI

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SEQUENCING OF NEW HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1) COMPLETE GENOMES BY ION TORRENT PLATFORM

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Background: The Human T-Cell Lymphotropic Virus Type 1 (HTLV-1) is the first human retrovirus isolated in 1980 and is associated with several etiologies as TSP/HAM (Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy), ATL (Adult T-cell leukemia/lymphoma) and HID (HTLV-1 associated infective dermatitis). It is estimated that approximately 5 to 10 million people are infected with HTLV-1 and this infection is worldwide distributed. Despite the clinical and epidemiological importance of HTLV-1 infection, there is a limitation of number of complete genomes available, about 0.12 complete genomes per 10,000 infected individuals and few studies related to the sequences (total and partial) available in the public databases. This study aimed to generate and characterize 31 HTLV-1 complete genomes sequences derived from individuals with different clinical status through the Ion Torrent sequencing platform. **Methods:** These sequences were assembled and analyzed. All the sequences were genotyped as Cosmopolitan subtype, Transcontinental subgroup. The genetic distance, showed low intragroup and intergroup diversity. The Geneious R6 software was used to analyze the non-coding region (LTR) to identify the transcriptions factors binding sites. **Results:** Our analyses demonstrated that two LTR mutations were able to abolish the binding of Sp1 (transcription factor). The same software was used to identify the variants at genome coding regions. No statistical relationship between variants and different clinical profiles (TSP/HAM, HID, ATL, Asymptomatic) were detected. The physico-chemical analysis showed that one mutation at env and gag genes was able to decrease the antigenicity while other mutation at gag gene (p24) was able to increase the antigenicity. The post-translational modification analysis demonstrated a low frequency of mutations associated with the creation or abrogation of these sites in different clinical profiles, with no statistical association. In a second phase of the study, we search the mutations found in the sequences generated in sequences previously published in Genbank, corroborating previous data, there was no statistical significance. **Conclusion:** This study contributed to increase of HTLV-1 complete genomes in world. Furthermore, to investigate better the contribution of HTLV-1 mutations for the disease outcome it is necessary evaluate the interaction of the viral genome and characteristics of the human host.

Key words: HTLV-1; genomes; sequencing; bioinformatic

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PLASMID CONSTRUCTION AND COMPARISON OF TWO DIFFERENT APPROACHES TO DETECT THE PROVIRAL LOAD OF PATIENTS INFECTED BY HTLV-1

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Background: HTLV-1 infection is endemic in Brazil, mainly in the Northeast region. Serological tests for virus detection often present inconclusive results, making it necessary to perform more specific confirmatory tests such as the polymerase chain reaction (PCR). PCR can also provide the proviral load of the subject, which is an important marker of prognosis, and has been associated with the development of HTLV-1-Associated Tropical Spastic Paraparesis / Myelopathy (HAM / TSP). Therefore, the aim of this study was to develop a protocol for the diagnosis and quantification of HTLV-1 proviral load of HTLV-1 infected patients treated at the Oswaldo Cruz University Hospital (HUOC) in Recife, by constructing a plasmid containing HTLV-1 sequence to be used as a positive control and for comparison of a direct and indirect quantitative analysis techniques. **Methods:** For this, the genic sequence of HTLV-1 was used as a template for the design of primers and specific probes. A sample from one HUOC patient with HTLV-1 infection confirmed by PCR was used to perform amplification of the pol gene of the virus by Nested PCR. The amplified 209bp gene fragment was cloned into the pGEM-T Easy® vector system (Promega) and the identity and integrity of the cloned DNA was confirmed by sequencing. The detection of the proviral load was then performed in DNA samples from 28 patients by quantitative PCR technique (qRT-PCR), using TaqMan® system and according to the protocol established by Adolfo Lutz Institute. The quantification was performed using a standard curve obtained from serial dilution of plasmid DNA and also, for comparison, by an indirect quantification method using the formula 2-CT target / 2-CT albumin x leukocytes x2 = copies of proviral DNA / mm3, previously described in the literature. **Results:** The proviral load values found by the two methods were very similar and did not differ statistically ($p = 0.66$). In addition, it was observed that patients with HAM / TSP had a high proviral load when compared to the asymptomatic group both by the standard curve method ($p = 0.01$) and by the method already established in the literature ($p = 0.01$). **Conclusion:** Therefore, the use of the plasmid developed in this study proved to be efficient as a positive standard for qRT-PCR in the diagnosis of HTLV-1, which is important for a better detection, characterization and clinical follow-up of patients with HTLV seen at HUOC.

Key words: HTLV-1; proviral load; plasmid construction

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DEVELOPMENT OF A POTENTIAL VACCINE CANDIDATE BASED ON MVA PLATFORM CODIFYING A MULTIEPITOPE CHIMERIC PROTEIN OF HTLV-1-HBZ

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Background: Human T-cell lymphotropic virus 1 (HTLV-1) is a retrovirus that belongs to the genus Deltaretrovirus and to the family Retroviridae. It is estimated that 5 to 10 million people living worldwide are infected with the virus, and about 5% of the patients will develop severe diseases. Two diseases are associated with the HTLV-1 infection, adult T-cell Leukemia (ATL) and HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). Although both diseases have poor prognosis, there is no specific treatment for them. Recently, studies have shown that the T-cell mediated cytotoxicity against the viral protein, HBZ, is able to control the infection. Due to the impact of the HTLV-1 infection, this project aims to construct a recombinant Modified Vaccinia Ankara (MVA) virus carrying a gene that codes a chimeric protein containing HBZ epitopes, as a potential candidate for HTLV-1 therapeutic vaccine. **Methods:** The epitopes contained in the chimera were selected through in silico analysis of T-cell epitope prediction. The chimera gene was commercially synthesized in the plasmid pCloneEZ and was amplified in E. coli XL10-Gold. The chimera gene was obtained from the pCloneEZ by restriction digestion with SmaI and PstI, and it was then subcloned in the transfer plasmid pLW44, which was also amplified in E. coli XL10-Gold. To generate the recombinant MVA, primary chicken embryo fibroblasts (CEFs) were infected with wild type MVA (m.o.i=1) and after adsorption the cells were transfected with 1000ng of pLW44. Clones of recombinant MVA were selected through detection of GFP, PCR and RT-PCR. **Results:** Two chimeric proteins (HBZ-CHI and HBZp-CHI) were constructed; the presence of a signal peptide (p) is the difference between them. Fragments of size of 294bp and 366bp, for the HBZ-CHI and HBZp-CHI, respectively, were observed after the digestion of the pCloneEZ and the subcloned pLW44. The PCR of the viral DNA has shown bands of 624bp and 692bp for HBZ-CHI and HBZp-Chi, respectively. Also, as expected, the RT-PCR of the viral RNA has shown a band of 267bp for both constructions. The viral sequences were confirmed by DNA sequencing by capillary electrophoresis. **Conclusion:** These results confirmed that recombinant MVA viruses carrying chimeric HBZ gene were built. Future studies should test the efficacy of these viruses as potential therapeutic vaccines for HTLV-1.

Key words: HTLV-1; potential vaccine; chimeric protein; HBZ

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PONTENTIAL ANTIVIRAL ACTIVITY OF MUSSISMILIA BRAZILIENSIS EXTRACT IN MT-2 CELLS

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Background: Mussismilia braziliensis (phylum Cnidarian, class Anthozoam, family Mussidae) is endemic in Brazil and is found along the coast of Bahia state. The potential antimicrobial activity of several cnidarian species against different microorganisms has been shown previously by others. However, M. braziliensis has never been tested as an antiviral agent. The present study aimed to investigate the potential antiviral effect of M. braziliensis coral extract in MT-2 cell lines permanently infected with HTLV-1. **Methods:** Coral extract from M. braziliensis was obtained and dissolved in RPMI. The antiviral activity was also evaluated using electron microscopy. The TEM analyses of MT-2 cells were performed 24 h post-incubation in the presence or absence of 80 mg coral extract. The analysis of TEM observed and quantified 419 virus particles: 384 viral particles were measured in cells treated with coral extract and 35 in untreated cells. **Results:** In the untreated cells, the virus particles ranged from 64 to 82 nm, and in the treated cells, they ranged from 38 to 65 nm. Comparison of treated and untreated cells by TEM shows that treatment with coral extract alters both the release of viral particles and the morphology, evidencing the production of defective particles. **Conclusion:** Hence, coral extract from M. braziliensis may inhibit viral replication in permanently HTLV-1-infected MT-2 cells, alters the morphology the particles viral it may be useful for development of new treatment for HTLV-1 infection.

Key words: HTLV-1; Mussismilia braziliensis; antiviral activity; extract; MT-2 cells

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SOROPREVALENCE AND GEOGRAPHICAL DISTRIBUTION OF HTLV IN BAHIA-BRAZIL

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Background: Human T-lymphotropic virus (HTLV) infection has a worldwide distribution, with prevalence varying according to the geographical region. It is estimated that in Brazil about 800,000 people are infected with this virus. Salvador, capital of Bahia state (northeastern Brazil), has been identified as the epicenter of HTLV-1 infection in the country with a prevalence of 1.76%. In this study, we attempted to estimate the seroprevalence and geographical distribution of HTLV in Bahia. **Methods:** This is a cross-sectional study conducted at the Central Laboratory of Public Health of Bahia (LACEN-BA). Search for all individuals for who HTLV serology was performed from January 1, 2004 to December 31, 2013 was done in LACEN-BA database using ETL (Extract, Transform, and Load) process. The key variable considered was register (unique for each individual). The diagnosis of HTLV infection was performed using chemiluminescence assays and was confirmed by Western Blot (WB) analysis. The municipalities of Bahia were classified according to the Regional Health Center (RHC). Samples with HTLV serology reagent without confirmatory WB were excluded from the analysis. **Results:** A total of 233,876 individuals were screened for HTLV serology; the mean age was 38±23 years, with a ratio female to male of 8 to 1. Individuals were from 394 out of 417 municipalities of Bahia (94.5%). HTLV chemiluminescence assay was found to be reagent for 3,025 individuals from whom 2,209 had WB results (1,978 positive, 62 negative and 282 indetermined). The HTLV type 1 (HTLV-1) was the most frequent (92%), followed by coinfection with HTLV-1/2 types (5%) and HTLV-2 (3%). Higher rates of HTLV infection was found in female with 30 to 50 years (44%). Cases of HTLV were found in 41% of municipalities. The global seroprevalence of HTLV infection was 0.9%, (95%CI, 0.8% - 0.9%) ranging from 0.2%, (95%CI, 0.2% - 0.3%) in RHC Centro Norte to 1.4% (95%CI, 1.2% -1.6%) in RHC Sul. Prevalence of HTLV infection in the RHC Leste was 1.3% (95%CI, 1.2 % - 1.4), highlighting Salvador with 1,4% (95%CI 1,3% – 1,5%). Ilhéus (RHC Sul) had the highest seroprevalence for HTLV 7.5% (95%CI, 6.2% - 9.0%). **Conclusion:** HTLV-infection is disseminated in Bahia, with a moderate rate of infection. It is estimated that approximately 140,000 individuals are infected with HTLV-1 in Bahia. Further studies should be conducted to better characterize the epidemiological and clinical profile of HTLV-infected individuals and to propose effective prevention measures.

Key words: HTLV, prevalence, Bahia.

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CHIMERIC PROTEIN (LVBA-RECHTLV-1/2) AS A POTENTIAL DIAGNOSTIC TOOL FOR HTLV-1 AND HTLV-2 VIRUSES

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INTRODUCTION

The diagnostic for HTLV-1/2 become mandatory in Brazil in 1993[3]. In the hemocenters it is performed through screening tests based on antibodies detection (ELISA), followed by a confirmatory test that might be based on antibodies detection (Western blot), and/or molecular detection (PCR)[14]. Indeterminate results pattern (positive on ELISA, Western blot with indeterminate pattern of bands and positive for PCR)[1] are the most challenging point in the diagnostic of infectious diseases both by the impact in different segments of Public Health, and for the individual itself, once it shows to have a direct relation with its health and well-being. Considering HTLV, this scenario is impacted by the fact that this infection is considered a neglected infection in Brazil, despite the large number of infected individuals.

The currently available kits of diagnostic indicate sensitivity and specificity above 99% (according to the manufacturer's instruction manual), nevertheless, studies performed in different cohorts in Brazil indicates a different reality. Two of them are highlighted here: the first one in Londrina (PR), where 27,9% of 49 HTLV positive individuals in ELISA test with HIV coinfection presented indeterminate pattern in Western blot assay[12]; and the second one in São Paulo (SP), were two confirmatory assays were performed with sera from 2,991 HTLV positive individuals, and the results showed 82,4% and 97,2% sensitivity and 60% and 80% specificity for Western blot and INNO-LIA, respectively[4]. These data point out that the available tests, both screening and confirmatory, do not exhibit the sensitivity and specificity indicated in the manufacturer's instructions manuals when used in Brazilian cohorts, emphasizing the necessity of establishing improvement in them.

According to new public policies and the necessity to provide screening diagnostic tests for HTLV-1/2 in public health services, this work aimed the development of a diagnostic tool based on multiepitope chimeric protein containing antigens for HTLV-1 and HTLV-2. Due the great number of testing and repetition for screening of infectious diseases in blood banks, the production of diagnostic tools based on national biotechnological is mandatory in Brazil, leading to the diminishing of the cost,

Submitted 03/23/2017, accepted for publication 09/06/2017 and published 09/29/2017
DOI: 10.17267/2317-3386bjmhh.v5i3.1341

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especially, but not only for HTLV-1/2 testing, that have its diagnostic based on imported kits. Another important point is that lowering the costs production, will bring a good impact on Brazilian public health, by allowing the screening of other impacting groups other than blood donors, as the pregnant women, diminishing the HTLV-1/2 viruses transmission.

MATERIALS AND METHODS

The multiepitope protein was designed for expression in prokaryotic vector and was based on molecules validated all around the world in ELISA and Western blot tests for HTLV-1 and HTLV-2: Env and Gag. In addition and according to our previous experience, the Tax protein epitopes were also included for both viruses. The search for these regions was based on scientific literature deposited in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), and then aligned in MultAlin platform (http://multalin.toulouse.inra.fr/multalin/) with Brazilian sequences deposited at GenBank (https://www.ncbi.nlm.nih.gov/genbank/). The chosen epitopes of Env, Gag and Tax protein were disposed in tandem, separated by flexible proline and glycine rings[11], in commercial pET32a+, an expression vector containing the gene codifying for histidine in C-terminus portion, in order to facilitate the protein purification. Escherichia coli Rosetta-gami 2(DE3) cells were transformed with this plasmidial vector and induced for 5 hours with IPTG 1mM. The protein was purified with affinity chromatography using sepharose His-Trap column and Äkta Start system.

In order to confirm the purification, a Western blot was performed in which 1000ng of the protein was transferred into a PVDF membrane, incubated for 16h at 4°C with commercial anti-histidine antibody (concentration used 1:1500), or pool of HTLV-1 infected individuals, pool of seronegative, or pool of HTLV-2 infected individuals (concentration used 1:100). After that, the membranes were incubated with secondary antibody anti-mouse IgG or anti-human IgG. The detection was performed using TMB substrate.

The sensitivity and specificity of the multiepitope protein was tested through an indirect ELISA developed in house, in which 96 flat bottom well polystyrene plates (Corning catalog number 9018) were coated using 150ng/well of the purified protein and incubated with sera of HTLV-1 or HTLV-2 infected individuals or seronegatives (1:50), followed by use of secondary antibody anti-IgG human labeled with peroxidase (1:25,000). The blocking agent was the low fat milk and the TMB substrate was used as a chromogenic substrate for protein detection, followed by reading at 450nm in spectrophotometer.

Statistical analysis were performed using GraphPad Prism 6.0, with OneWay ANOVA test and Tukey post test or t-test. A receiver operating characteristic curve (ROC curve), statistical tool to evaluate the global accuracy of the test applied to the identification of the infected individuals15, were accomplished through the same software. Each point in the graph represents the values of the referred index, in different cut-offs, determining the area under the curve, the global accuracy indicator of the test[19].

The study population consisted in samples of peripheral blood from individuals infected with HTLV-1 or HTLV-2 and non-infected individuals, submitted to clinical and laboratorial evaluation performed at Fundação Hemominas and Rede Sarah de Hospitais do Aparelho Locomotor, both in Belo Horizonte, Minas Gerais. The positive individuals for HTLV-1 and HTLV-2 analyzed by ELISA, Western blot and PCR were invited to participate in the survey by Fundação Hemominas. Those that agreed, signed a Consent Term and were clinically evaluated for several medical specialties. This project was approved by UFMG Ethics Committee (CAAE - 55618516.1.0000.5149) and by Fundação HEMOMINAS Ethics Committee in Research (CAAE 55618516.1.3001.5118). In addition to GIPH patients, sera samples gently provided by Dr Adele Caterino de Araújo (Instituto Adolf Lutz; CCD-SES/SP, FCF-USP) from São Paulo state cohort, and by Dr. Antonio Carlos Rosário Vallinoto, from Laboratório de Virologia at Instituto de Ciências Biológicas, Universidade Federal do Pará, were also evaluated in this work.

RESULTS

According to literature reviewed and published in the nineties[8, 9, 10], it was possible to observe that Gag, Env and Tax proteins of HTLV-1 and HTLV-2 viruses are widely used in diagnostic systems for the detection of these viruses, what guided the search of antigenic epitopes in this work.

Gag protein is cleaved into protein fragments p15, p19 and p24 that are well characterized as antigens. A long-term study performed at Fundação HEMOMINAS with 60 blood donors candidates showed that the positivity only for p24 protein band at Western blot was the most frequent indeterminate pattern (54,2%). In addition, this study showed that the reactivity of only Gag proteins, without positivity for Env proteins, exhibited indeterminate results in these tests[13]. Therefore, p24 protein was not considered in the in silico analysis to be incorporated in the chimeric protein.

In relation to glycoproteins gp46 and gp21, the recombinants derived of gp46 would be good candidates to compose a serological screening test6. However, recombinant protein rgp21 combined with p24 protein is largely related to high levels of false-positive results9. Some commercial diagnostic kits use the recombinant protein p21 and GD21, that are linked to indeterminate results patterns (for example HTLV Blot 2.4, MP Diagnostics), and, therefore, gp21 was not included in the chimera.

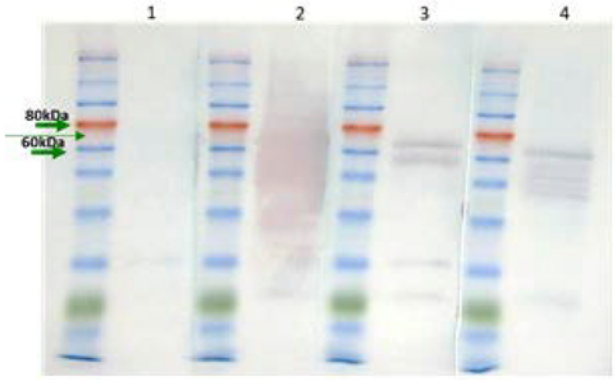
Our research group confirmed that the C-terminal portion of the Tax protein has great antigenic importance in the recognition of anti-HTLV-1 antibodies not only in HAM / TSP individuals but also in asymptomatic patients, verifying that Tax protein can be used as a diagnostic tool , but can also be used as a biomarker for the progression of disease in patients infected by HTLV-1[16, 17].

For reasons of intellectual property protection, the sequences used in the construction of this chimera are not presented. After constructing the gene cassette, expressing and purifying the protein, preliminary Western blot assays showed that the LVBA-recHTLV-1/2 chimera is recognized by antibodies from individuals infected by HTLV-1 or HTLV-2, which was not observed for the seronegative individuals for HTLV-1/2 (figure 1).

The indirect ELISA in house assays were performed using the set of samples from Table 1: 55 HTLV-1 positive samples, 25 HTLV-2 positive samples and 55 HTLV-negative samples (all of them confirmed by HTLV Blot 2.4). The data groups were analyzed in four different ways to obtain a better comparison of the data (figure 2). The sensitivity and specificity data provided by the ROC curve were used to define the test cut-off value (0.3615). The specificity value was close to 91% (90.91%) and the highest possible sensitivity value (96.39%). In addition, the data were plotted in the separate groups: symptomatic and asymptomatic HTLV-1, HTLV-2 positive and HTLV-negative (Figure 2a); HTLV-1 positive (symptomatic and asymptomatic), HTLV-2 positive and HTLV-negative (figure 2b); HTLV-positive (HTLV-1 and 2 together) and HTLV-negative (Figure 2c); and, ROC curve (figure 2d). It is possible to observe in results, that the recombinant LVBA-recHTLV-1/2 protein was recognized by IgG from HTLV-1 and HTLV-2 infected individuals with statistical difference ($p < 0.0001$) from uninfected individuals. Moreover, the antigens used obtained high accuracy according to the area on the curve of the ROC statistic[19].

Figure 1. Western blot of purified LVBA-recHTLV-1/2 protein. 1) seronegative pool; 2) positive HTLV-1 pool; 3) positive HTLV-2 pool; 4) anti-histidine. The green fine arrow indicates approximate molecular weight of 70 kDa, corresponding to the size of the purified protein. It is possible to observe the multiepitope protein was detected by sera pool of individuals infected with HTLV-1, HTLV-2 and wtih the commercial anti-histidine antibody. The pool of seronegative individuals did not react with the target protein.

Anti-LVBA-recHTLV-1/2 IgG response in Western Blot



1- Pool of seronegative 1:100 / anti-human IgG 1:2000
2- Pool of HTLV-1 positive sera 1:100 / anti-human IgG 1:2000
3- Pool of HTLV-2 positive sera 1:100 / anti-human IgG 1:2000
4- Anti-his 1:1500 / anti-mouse IgG 1:10000

Figure 2. Detection of the chimeric LVA-recHTLV-1/2 chimeric protein by human IgG from individuals infected or not by HTLV. A) Absorbance values of individuals infected with HTLV-1 symptomatic (with HAM / TSP) and asymptomatic, HTLV-2 or uninfected; B) Symptomatic and asymptomatic positive HTLV-1 individuals represented as a single group; C) representation of positive and negative HTLV individuals; D) ROC curve. AUC: area under curve. Graphs A and B were statistically treated with OneWay ANOVA test and Tukey multiple comparisons test; and, the graph C with t test. *: p <0.05; ***: p <0.001; ****: p <0.0001. The green frame in the graphs A, B and C correspond is related to the cut-off area (0.3615), which corresponds to specificity 90.91% and sensitivity 96.39%, determined by the ROC curve. The results shown a statistical difference with p<0.0001 between infected and uninfected individuals, regardless of the way the data are analyzed.

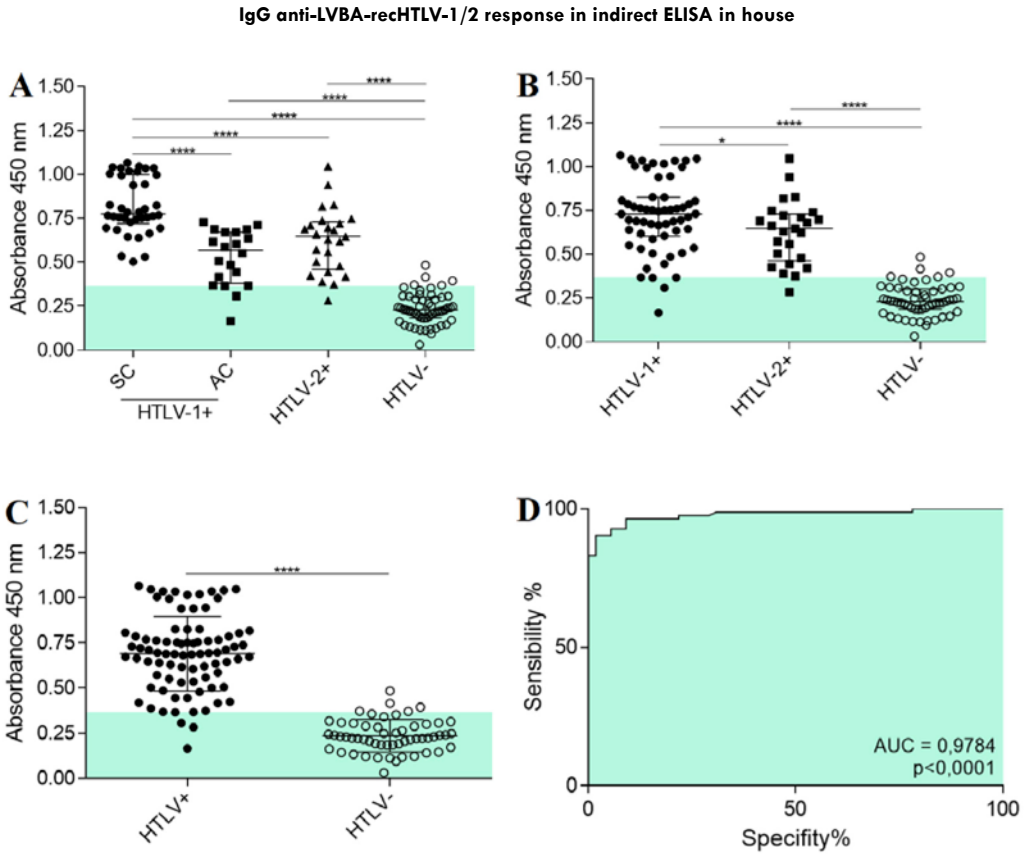


Table 1. Characteristics of the HTLV-1 and HTLV-2 samples used in the indirect ELISA in house.

Cohort	HTLV-1	Cohort	HTLV-2	HTLV+	HTLV-
GIPH (Asymptomatic)	20	GIPH	5		
GIPH (HAM/TSP)	38	SP	10		
		PA	10		
Total	**58**		**25**	**83**	**55**

GIPH: Grupo Interdisciplinar de Pesquisa em HTLV - Fundação HEMOMINAS; SP: São Paulo; PA: Pará; HTLV+: total of HTLV positive samples; HTLV-: total of HTLV seronegative samples.

DISCUSSION

The ROC statistic determined the cut-off of 0.3615 for indirect in house ELISA using the multiepitope protein (LVBA-recHTLV-1/2). Although this cut off value can considered high and still include positive samples, this value is lower than that used by Jacob et al., (2007)7, when testing seven different EIA kits with 2,312 samples from individuals from the state of São Paulo (cut-off = 1.0). In the EIA kit containing recombinant antigens (Murex HTLV-I + II, Murex Biotech) with this same group of patients, the sensitivity was 94.2% and the specificity was 46.7% when compared to WB 2.4 (HTLV blot 2.4, Genelabs Diagnostics, gold standard in the diagnosis of HTLV seroreactive samples). It should be noted that the sensitivity and specificity (96.39% and 90.91%, respectively) reached exceed those obtained by the Murex test, which is very promising for the development of a new diagnostic system.

Caterino-de-Araujo (2009)5 described the importance of an effective diagnostic system in Brazil. Two ELISA systems with different compositions of antigens and formats were compared in Brazil, in contrast to a work done in Argentina that compared two ELISAs and one PA (particle-agglutination). The results showed that the worst performance of the ELISA assay for the Argentine cohort was the most sensitive and specific in Brazil (namely the Vironostika HTLV-1/2 kit, bioMerieux, Boxtel, The Netherlands). In addition, the Western blot used in the confirmatory test (HTLV blot 2.4, Genelabs Diagnostics, Science Park, Singapore) presented results with high serum levels and does not accurately detect HTLV-1/2 in infected patients[7, 2, 5].

HTLV screening tests have undergone constant changes due to modification in algorithms and discontinuation of available assays. The HTLV diagnosis situation is further aggravated by the fact that only one test, used as a confirmatory test (HTLV blot 2.4), is licensed by the FDA (Food and Drug Administration) and, for research, although it is commercially sold worldwide. Then, the development of a diagnostic system with high performance in sensitivity and specificity is the direction to beneficially alter the diagnostic routine, being capable of confirming and discriminating HTLV-1 and HTLV-2[18].

The chimeric LVBA-recHTLV-1/2 antigen was capable of detect with sensitivity and sensibility antibodies anti-HTLV-1/HTLV-2 present in the serum of individuals infected and belonged Minas Gerais, Pará and São Paulo States, showing high accuracy in the preliminary tests performed. Thus, the LVBA-recHTLV-1/2 chimera is very promising for advance in the HTLV-1 and HTLV-2 diagnosis.

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TOPOGRAPHIC, SYNDROMIC DIAGNOSIS AND PATHOPHYSIOLOGICAL MECHANISM MAY DIFFERENTIATE THE HAM/TSP FROM OTHER MYELOPATHIES

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INTRODUCTION

Knowledge about HTLV-1 and its association with disease has been increasing since its isolation in 1980.[1] HAM/TSP (HTLV-1-associated Myelopathy/Tropical Spastic Paraparesis) remains the classical neurological disease associated with this infection since 1985.[2] HAM/TSP diagnoses criteria defined by WHO (1988) and Castro-Costa et al. (2006) are well established and are the most used in the definition of the neurological disease associated with this virus.[3,4]

The HTLV-1 Interdisciplinary Research Group (GIPH) has followed individuals infected with HTLV-1 since 1997 and has observed, as well as other groups and authors, that some HTLV-1 infected individuals have symptoms and neurological signs that do not meet the full criteria referred to above.[5,6,7]

The diagnosis of central nervous system involvement by HTLV-1 is difficult due to a long latency between infection, the onset of the first symptoms and signs, to defined HAM / TSP. HTLV-1 neurological impairment prevalence may be underreported. Incomplete clinical manifestations for HAM/TSP diagnosis are not considered in most clinical and epidemiological studies, which can contribute to mask the real impact of this infection in população.[8]

The knowledge obtained in the literature in association with the experience of 20 years of follow-up of individuals infected by HTLV-1 in the GIPH cohort allowed us to propose a topographical, syndromic diagnosis and a pathophysiological mechanism that differentiate HAM / TSP from other infectious, inflammatory and metabolic myelopathies.

We believe that our proposal may facilitate the understanding and diagnosis of HAM / TSP and other CNS disorders without defined criteria for HAM / TSP, as well as open perspectives for new studies on the pathogenesis and treatment of neurological diseases associated with this infection.

MATERIAL E MÉTODOS

This is a narrative review that originated in some questions during the follow-up of HTLV-1

Submitted 03/23/2017, accepted for publication 09/06/2017 and published 09/29/2017
DOI: 10.17267/2317-3386bjmhh.v5i3.1341

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infected individuals of the GIPH cohort: 1- Why does a systemic infectious disease preferentially affect the thoracic spinal cord more strongly? 2- Why did HTLV-1 infected individuals present hypometabolism in the thoracic spinal cord and other segments of the central nervous system in an evaluation with 18-F FDG PET/CT?

The literature search was oriented on the four topics described below:
1- Topographic evidence and findings in HAM/TSP autopsy studies;
2- Find an explanation for the major impairment of the thoracic spinal cord in HTLV-1 infection;
3- Find a clinical and anatomical neurological correlation in CNS impairment by HTLV-1;
4- Differentiate the HAM/TSP from other myelopathies based on the proposal of topographic, syndromic diagnosis and the pathophysiological mechanism considered in the present review.

RESULTS

Autopsy study of two HAM / TSP patients published in 1992, with a subsequent review of the literature by the same author in 2010, which describes the findings observed in 30 HAM/TSP individuals autopsies, report the involvement of the central nervous system (CNS) in its entirety, but with greater intensity at the level of the thoracic spinal cord in its middle and lower portion. In these more intensely affected segments, the central portion of the lateral funiculus, intermediate areas between the central and peripheral irrigation (watershed) of the thoracic spinal cord were also described as the most compromised areas.[9,10]

The spinal cord presents a disproportionate vascularization between the cervical, thoracic, lumbar and sacral segments. At the middle and lower thoracic levels the caliber of the anterior spinal artery gradually reduces in the cranio-caudal direction, with consequent reduction of tissue vascularization and irrigation by the central artery of the spinal cord. The central artery the thoracic spinal cord is still responsible for irrigating a larger area compared to the other CNS segments of the spinal cord.[11] The lateral fasciculus in its most central portion (watershed area) is the most impaired in relation to flow deficit and blood irrigation, coinciding with the most affected areas of the thoracic spinal cord described in HAM / TSP autopsy studies.

Why is the thoracic spinal cord the initial and most compromised CNS segment by HTLV-1? We know that only some types of human body cells are infected by HTLV-1 and that the infection of these cells is related to the presence of cell surface proteins, HSPG (heparan sulfate glycoprotein), NRP-1 (neuropilin-1) and GLUT-1 (glucose transporter type 1), important for binding of infected cells to target cells and virus entry.[12] Afonso et al., 2008, demonstrated that endothelial cells from the blood-brain barrier of the thoracic and brain express the receptors necessary for HTLV-1 entry, and that the permeability of the blood-brain barrier is compromised when these endothelial cells become infected and with endothelial cell infection the permeability of the blood-brain barrier is altered, allowing the passage of infected and uninfected lymphocytes into the CNS.[13]

But why are watershed areas of CNS more affected by HTLV-1? The possible link found by us to explain this question was that CNS áreas susceptible to hypoxia express more angiogenic factors. VEGF 165 (vascular endothelial growth factor) one of the most important factors in the expression of angiogenesis has as main co-receptors the HSPG and NRP-1 proteins.[14,15] The knowledge previously discussed allowed us to define the exact CNS region preferentially affected by HTLV-1. We then found a strong anatomic-clinical correlation between involvement of the central portion of the lateral fasciculus (watershed area) and HAM/TSP clinical presentation. This anatomical-clinical correlation allowed us to define a topographic and syndromic diagnosis for HAM/TSP. Figure 1 shows the main tracts and fibers of the watershed area of the lateral fasciculus.[11] Corticospinal and rubrospinal tracts stimulate flexor motor neurons and inhibit extensors motor neurons. Reticulospinal and fastigiospinal fibers help in the maintenance of the posture, stimulating extensor motor neurons and inhibiting the flexors motor neurons. The impairment

these tracts and fibers are responsible for the clinical presentation of paraparesis, spasticity, gait changes and pyramidal signs observed in HAM/TSP. Rafespinal fibers modulate nociceptive transmission and their involvement may explain the chronic pain symptoms frequently observed. The hypothalamic spinal fibers modulate visceral efferent motor neurons and their impairments explain urinary, intestinal and sexual autonomic dysfunction.[16] Other tracts and fibers present in this level of the thoracic spinal cord, outside the watershed zone: posterior column (gracile and cuneiform fascicles), lateral peripheral region (anterior and posterior spinocerebellar tracts, anterolateral system) are apparently preserved in HAM/TSP and symptoms and clinical signs that demonstrate the impairment of these tracts and fibers are not present in most carriers of the disease.

Considering the facts presented, the differential diagnosis of HAM/TSP in relation to other myelopathies became more feasible based on topographic, syndromic, clinical diagnoses and the pathophysiological correlation presented. Table 1 summarizes the topographic, syndromic and clinical presentation of the most prevalent myelopathies.[17]

DISCUSSION

Our proposal covers two distinct points in human HTLV-1 infection: diagnosis and pathogenesis. The correlation observed between these two points led us to present them together.

We observed that areas of the CNS that are more susceptible to hypoxia (watershed) are more compromised in human HTLV-1 infection as reported in autopsy studies of HAM/TSP carriers. Considering anatomical aspects, the thoracic spinal cord is the segment of the CNS most susceptible to hypoxia in detriment of its reduced vascularization. Hypoxia in these areas would stimulate the expression of angiogenic factors, emphasizing VEGF165. VEGF165 is linked to endothelial cell wall co-receptors, HSPG and NRP-1. These surface proteins are also involved in the entry mechanisms of HTLV-1 in the target cell, which binds its surface unit to these two proteins, leading to conformational changes of the virus that enable it to enter the target cell using GLUT-1. Most segments of the CNS presented good blood perfusion and have low angiogenesis. Watershed areas of the brain are also affected by HTLV-1 as described in autopsy, imaging and PET/CT studies.[18,19] Endothelial cells from the blood-brain barrier of the thoracic and brain express the receptors required for the entry of HTLV-1 and infection of these cells would lead to changes in the permeability of the blood-brain barrier, passage of infected and uninfected lymphocytes into the CNS, and onset of a immune-mediated process associated with localized impairment.

We know that the pathogenesis of HTLV-1 is complex and involves other processes not considered in this review and that need to be considered in association with our propositions.

We emphasize the importance of this topographic, syndromic, clinical and pathophysiological correlation in CNS involvement in HTLV-1 infection. We believe that this knowledge may be expanded to explain the genesis of other known neurological and systemic disorders described in HTLV-1 infection.

In our understanding, the diagnostic criteria for HAM/TSP considered by WHO and Castro-Costa et al., 2006 for HAM/TSP defined are correct and should be maintained, but neurological symptoms and signs that do not meet the criteria for defined HAM/TSP, corresponding to the more restricted involvement of the thoracic spinal cord or of other CNS segments impairment, they need more precise and defined diagnostic criteria. The possible and probable HAM/TSP terms create doubt in the relation of clinical manifestation and HTLV-1 infection. We believe that in the endemic areas, the diagnosis of these neurological manifestations that do not meet the criteria for defined HAM/TSP are important to define the real morbidity and greater suspicion of HTLV-1 infection in infected individuals who do not now their condition. We believe that our considerations may bring greater understanding and facilitate the diagnosis of neurological diseases associated with HTLV-1 infection.

Figure 1. Vascularization of lumbar spinal cord. Contribution of the ASA and PSA in supplying the blood to the spinal cord. Modified with permission form Nicholas Theodore, M. D.

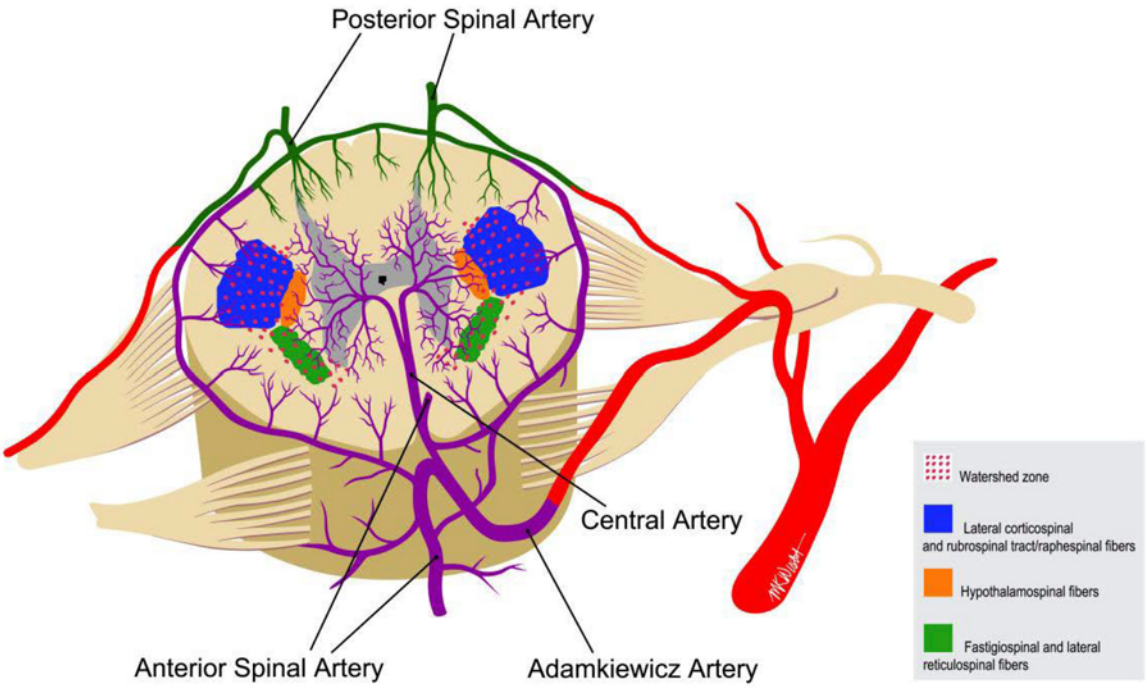


Table 1. Differential diagnosis of myelopathies (to be continued)

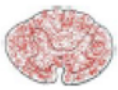
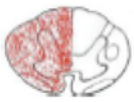
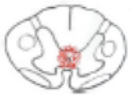
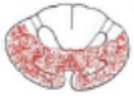
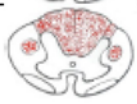
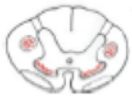
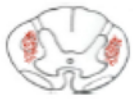
Topographic spinal cord syndromes	Illustration	Clinical symptoms	Diseases and presentation
Complete		- Complete loss of spinal cord function below the affected segment with pyramidal, sensory and autonomic dysfunction	- Acute compressive lesion - Necrotizing myelitis - Trauma (Acute)
Brown-Séquard		- Loss of pain and temperature sense on the side of the lesion - Pyramidal weakness and loss of vibration and joint position sense the opposite side of the lesion	- Multiple sclerosis - Myelitis (Viral; autoimmune) (Subacute) - Compressive disorders (Acute; Subacute)
Central		- Autonomic dysfuntion - Spinothalamic deficits - Pyramidal weakness below the level of the lesion	- Syringomyelia (Chronic) - Optic neuromyelitis (Acute)
Anterior		-Acute flaccid weakness - Spinothalamic dysfunction - Preserved dorsal column function	- Spinal artery occlusion (Acute)
Posterior		- Isolated loss of vibration and joint position sense	- Neurosyphilis (Tabes dorsalis) (Subacute; Chronic)
Posterolateral		- Loss of vibration and joint position sense - Pyramidal involviment	-Vitamin B12, copper deficiency (Subacute)

Table 1. Differential diagnosis of myelopathies (conclusion)

Topographic spinal cord syndromes	Illustration	Clinical symptoms	Diseases and presentation
Other isolated tract involvements		- Isolated tract involvement other than dorsal columns - cortico spinal tract is most commonly involved	- Paraneoplastic (Subacute) - Motor neuron diseases (Subacute; Chronic)
Watershed zone anterior circulation		- Spastic paraparesis - Pyramidal signs - Urinary, sexual and bowel dysfunction - Low back and lower limbs pain	- HAM/TSP (Chronic)

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PROPOSAL OF AN ALGORITHM FOR THE DIAGNOSIS OF DRY EYE DISEASE IN INDIVIDUALS INFECTED WITH HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1

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INTRODUCTION

Human T-cell Lymphotropic Virus type 1 (HTLV-1) is the etiologic agent of adult T cell leukemia (ATL)[20], tropical spastic paraparesis/ HTLV-1-associated myelopathy (HAM/TSP)[5] and infective dermatitis in children[2]. An ophthalmologic disease, HTLV-I-associated uveitis (HAU) is also linked to HTLV-1 infection[11]. In addition, other ophthalmologic alterations such as corneal lesions, retinal vasculitis and keratoconjunctivitis sicca (KCS) or dry eye disease (DED) are also associated with HTLV-1[7,9]. In these individuals, the prevalence of DED may reach 30-40%[13], especially in symptomatic patients with HAM/TSP.

DED is an ocular surface disease that causes eye discomfort, visual disturbance, and tear film instability[6,17]. The mechanism leading to DED in HTLV-1-infected persons remains unclear. It is reported that antinuclear antibodies, present in autoimmune diseases, such as rheumatoid factor, anti-SSA/Ro and anti-SSB/La are absent in patients with DED diagnosis associated with HTLV-1[4]. Conversely, there was an association between high HTLV-1 proviral load (PVL) and DED in infected patients[4].

Complaints suggestive of DED are blurred vision, dryness, foreign body sensation and burning eyes. To confirm the diagnosis, it is mandatory to both measure the volume and evaluate the quality of tears. The three most widely used tests for assessment of dry eye are the Schirmer I test, tear breakup time test (TBUT) and Rose Bengal staining. The Schirmer I test measures the basal and reflex tear secretion. TBUT is used to assess tear film stability. The Rose Bengal staining evaluates both conjunctival and corneal damage. However, this test has the disadvantage of being toxic and causing typical burning[14]. In addition, patients' complaints might be evaluated by means of the Ocular Surface Disease Index (OSDI). The OSDI is a specific questionnaire that provides a rapid assessment of dry eye symptoms and their impact on vision-related functioning[15].

In general, studies have combined symptoms questionnaires and two or three tests to evaluate the volume and the quality of tears. However, no definite protocol for DED diagnosis has been proposed and there is poor relation between symptoms and diagnosis tests[16]. The aim of the present study was to evaluate the accuracy of TBUT, Schirmer I test, Rose Bengal

Submitted 03/23/2017, accepted for publication 09/06/2017 and published 09/29/2017
DOI: 10.17267/2317-3386bjmhh.v5i3.1341

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staining and OSDI, alone or combined, for the diagnosis of DED in HTLV-1-infected individuals; and to propose an algorithm for DED diagnosis with low cost and minimally invasive procedures.

METHODS

A prospective study was conducted at the Bahiana School of Medicine and Public Health reference center for HTLV, Salvador, Bahia, Brazil, between February 2013 and November 2013. Patients were sequentially invited to the ophthalmological clinic at the time of their routine medical visit. They were eligible if they had a positive serological diagnosis of HTLV-1 (ELISA and Western Blot). Patients presenting any previous palpebral disorders, intraocular surgery and who had nasolacrimal duct obstruction were excluded. The Institutional Research Board of Bahiana School of Medicine approved the study and all patients signed an informed consent.

Ophthalmologic examination and measurements. Patients underwent a detailed ophthalmic examination, including best-corrected visual acuity, intraocular pressure measurement with applanation tonometer, anterior segment, and fundus examination with a slit-lamp biomicroscope. First, all patients were evaluated for clinical symptoms using the OSDI. This questionnaire has been validated in Brazil[12] and provides a rapid assessment of the symptoms of ocular irritation consistent with DED. Patients were classified on a scale of intensity for dry eyes as normal, mild, moderate and severe condition, according to the score obtained in OSDI. Then, tear secretion of both eyes was evaluated, using the three following tests: TBUT, Schirmer I test and Rose Bengal. TBUT was performed by instillation of 1% fluorescein solution (Colírio de Fluoresceína®; Ophtalmos®, São Paulo, Brazil) and the time required for dry spots to appear on the corneal surface after blinking was measured. Dry spots that appeared in less than 10 seconds were considered abnormal. To perform the Schirmer I test, millimeter Whatman strips (Teste de Schirmer®, Opthalmos®,São Paulo, Brazil) with 5mm x 35mm were placed in the lower fornix near the lateral canthus of both eyes. After 5 minutes, the strips were removed and the wet portion was measured. A result less than 5mm was considered abnormal. The Rose Bengal test was performed with 1% rose bengal staining solution (Colírio de Rosa Bengala®; Ophthalmos®, São Paulo, Brazil), and was considered abnormal when its total score was higher than three points[18]. DED was diagnosed when at least two of these three tests were abnormal.

Statistical Analysis: Age was expressed as means (SD) and gender and presence of DED were expressed as relative frequency. Means comparison was performed using t-tests or Mann–Whitney tests according to Gaussian or non-Gaussian statistical distribution. Sensitivity, specificity, positive and negative predictive value and overall accuracies (OA) of each test alone were calculated using the OpenEpi software program version 3.01[19]. Two tests at a time were combined in parallel and series to evaluate the ability to differentiate persons with dry eye from normal individuals. When combined in parallel, only one positive result is sufficient. When combined in series both tests must be positive. The MS-excel software program was used to calculate accuracy. All statistical analysis was carried out using SPSS/PC Statistical Software Program Version 18.0 (SPSS, Chicago, IL)

RESULTS

Ninety-six subjects were included in the study; 71 (74%) were female. Fifty patients (52.1%) had a diagnosis of DED. The mean age for patients with DED diagnosis was 53.6 years and for patients without DED, 47.4years, which was statistically significant($p=0.017$). The age for all patients ranged from 23 to 78 years.

Sensitivity, specificity, positive and negative predictive value and overall accuracies of each test alone and combined in parallel or in series are represented in Table 1.

Table 1. Effectiveness of tests used to evaluate KCS in HTLV-1 patients.

TEST	SENS (%)	SPEC (%)	False-Neg	False-Pos	PPV (%)	NPV (%)	OA (%)
OSDI	75.0	51.2	31.3	41.2	58.8	68.8	62.7
TBUT	98.0	69.5	3.0	22.2	77.8	97.0	84.4
SCH	44.0	100	37.8	0.0	100	62.2	70.8
RB	87.8	89.7	14.6	8.1	91.5	85.4	88.6
Combined Tests (Parallel)							
OSDI or TBUT	99.5	35.6	1.5	37.3	62.7	98.5	
OSDI or SCH	86.0	51.2	22.9	62.8	37.3	77.1	
TBUT or SCH	98.9	69.6	1.7	22.1	78.0	98.3	
OSDI or TBUT or SCH	99.7	35.6	0.8	37.3	62.7	99.2	
Combined Tests (Series)							
OSDI and TBUT	73.5	85.1	25.3	15.7	84.3	74.7	
OSDI and SCH	33.0	1.0	42.2	0.0	1.0	57.9	
TBUT and SCH	43.1	1.0	38.2	0.0	1.0	61.8	
OSDI and TBUT and SCH	37.8	100	40.3	0.0	100	59.7	

Keratoconjunctivitis sicca (KCS); Human T-cell Lymphotropic Virus type 1 (HTLV-1); Sensitivity (SENS); Specificity (SPEC); False-negatives (False-Neg); False Positives (False-Pos); Positive Predictive Value (PPV); Negative Predictive Value (NPV); Overall Accuracies (OA). Tear Break Up Time (TBUT); Schirmer (SCH); Rose Bengal (RB); Ocular Surface Disease Index (OSDI).

When evaluated alone, the most sensitive test was TBUT (98.0%), presenting a false-negative rate of 3.0%, and 69.6% of specificity. The Schirmer I test was the most specific (100%) with absence of false-positives cases; the sensitivity was 44.0%. The highest overall accuracy of sensitivity and specificity was found for rose bengal (88.6%),while OSDI had the lowest (62.7%) overall accuracy.

Combined in parallel, TBUT and OSDI were the most sensitive (99.5%), followed by the combination of TBUT and Schirmer I test (98.9% sensitivity), with a false positive rate of 37.3% and 22.1%, respectively. The specificity of both combinations was 35.6% and 69.6%, respectively. The association of the TBUT, Schirmer I test and OSDI showed the highest sensitivity and 35.6% specificity.

Combined in series, a positive Schirmer I test, combined with a positive TBUT or OSDI, reached a specificity of 100%, with 43.1% and 33.0% sensitivity, respectively. The TBUT, Schirmer I test and OSDI combined showed 100% specificity and 37.8% sensitivity.

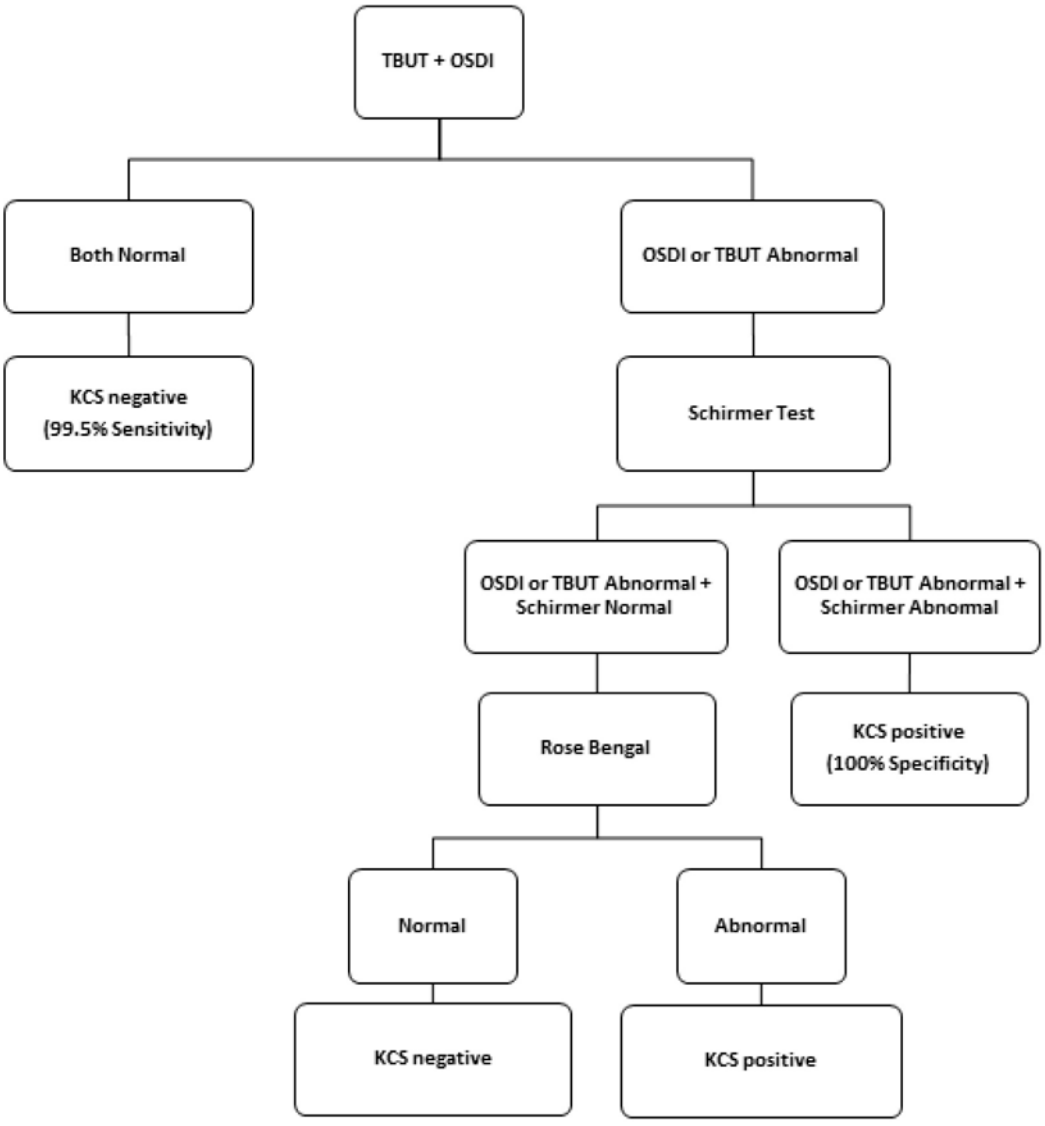
DISCUSSION

The results presented herein refer to the assessment of the efficacy of low cost tests widely used for the diagnosis of DED in a group of HTLV-1-infected patients. When evaluated alone, TBUT proved to be the best screening test, with the highest sensitivity and negative predictive value. However, for confirmation of the diagnosis, additional tests were required. The Schirmer I test had the highest specificity (100%), making this test essential for confirmation of DED diagnosis. In the present study, the Schirmer I test showed a sensitivity of less than 50%, similar to sensitivity rates described in the literature[3]. Rose Bengal staining presented the best overall accuracy. However, when evaluated alone, Rose Bengal did not provide high positive and negative predictive values. Therefore, the use of this test only is not suitable for the purpose of confirming or excluding the diagnosis of DED. Moreover, patients usually complained of itching and redness, and in some cases, severe ocular inflammation after the test. In spite of this dye being a derivative of fluorescein, which is harmless, it has a dose-dependent toxic effect on human corneal epithelial cells in vitro[8]. Due to the side effects, the use of Rose Bengal dye should be limited to patients for whom the DED diagnosis was not conclusive. The Rose Bengal also could be replaced by Lissamina Green, a dye that is well tolerated and is equally effective as Rose Bengal in evaluating the ocular surface[10].

As regards the effectiveness of the OSDI, its accuracy was very low when the questionnaire was considered alone for the diagnosis of DED. This demonstrated the weak correlation between the patient's symptoms and clinical signs, particularly in mild-moderate DED.

Serial testing maximizes specificity and positive predictive value but decreases sensitivity and the negative predictive value. Multiple tests combined in parallel increase the sensitivity, and therefore, the negative predictive value. Instead performing all tests in all patients, the diagnostic algorithm proposed in the present study follows a sequence based on the performance of the tests in three stages. Based on the results obtained herein, we suggest an algorithm for screening HTLV-1-infected patients and making a reliable diagnosis of KCS (Figure 1). Firstly, all infected patients would be screened using both the OSDI questionnaire and TBUT. If both tests are normal, dry eye diagnosis might be excluded. Secondly, if the OSDI questionnaire and/or TBUT are abnormal, the Schirmer I test must be performed for all patients. A positive Schirmer I test confirms the KCS diagnosis. Thirdly, in those patients for whom the diagnosis remains indeterminate (Schirmer I test negative), Rose Bengal staining must be performed. Although 100% predictive positive value was found for several test combinations evaluated in this study, none of them was sufficient to completely exclude the occurrence of false negatives. Therefore, in patients with HAM/TSP diagnosis, with HTLV-1 proviral load of over 10% of infected cells, or those older than 45 years, the Rose Bengal test should be considered, despite a negative result for the TBUT, OSDI and Schirmer test.

Figure 1. Algorithm for KCS diagnosis in HTLV-1-infected patients.
Keratoconjunctivitis sicca (KCS); Human T-cell Lymphotropic Virus type 1 (HTLV-1); Tear Break Up Time (TBUT); Ocular Surface Disease Index (OSDI);



One limitation of the present study is that the proposed algorithm cannot to distinguish DED as an aqueous deficient dry eye (ADDED) or an evaporative dry eye (EDE). However, it is probable that DED in patients infected with HTLV-1 is mainly due to the viral damage on the lacrimal gland, resulting in a decreased tear production[1]. In addition, Meibomian gland disease, which is the most common form of EDE, might be easily excluded by examination of structures of the eye with a biomicroscopy.

In summary, this study demonstrated that a reliable DED diagnosis in HTLV-1 patients could be made, using tests to evaluate dry eye and a validated questionnaire, not only as information about the patients' complaints, but also as part of diagnosis algorithm. The algorithm described might be useful for diagnosis of moderate/ severe ADDE. This would allow the exclusion of patients in whom it is possible to confirm or to exclude DED diagnosis before the next step, therefore, this algorithm might contribute to reducing costs, discomfort for the patient and time, without compromising the diagnostic efficacy.

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ESTIMATIVA DO NÚMERO DE CASOS DE INFECÇÃO POR HTLV-1 ATRAVÉS DE TRANSMISSÃO VERTICAL NO BRASIL POR ANO

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INTRODUÇÃO

Estima-se que cerca de 5-10 milhões de indivíduos no mundo estejam infectados pelo vírus HTLV. O Brasil é o país com maior número absoluto de infecções, apresentando aproximadamente 800 mil portadores[1]. Este vírus pode ser transmitido por via sexual, por contato com sangue infectado e de mãe para filho, principalmente através do aleitamento[1].

A maioria dos indivíduos infectados permanece assintomática (cerca de 95%). Estes tornam-se reservatórios para o vírus, perpetuando a cadeia de transmissão. Por outro lado, as doenças associadas a esta infecção, como a mielopatia associada ao HTLV-1/ paraparesia espástica tropical (HAM/TSP) e a leucemia de células T do adulto (ATL) apresentam elevada morbidade e mortalidade[1–3]. O tratamento para estas condições clínicas ainda é limitado. Sendo assim, a prevenção da infecção é de suma importância.

Com o intuito de reduzir a transmissão deste vírus no Brasil, desde 1993 as amostras de sangue são testadas antes de hemotransfusão[4]. No entanto, atualmente, a testagem para a infecção pelo HTLV não está incluída dentre os exames realizados no pré-natal do Sistema Único de Saúde (SUS) do Brasil. Assim, a transmissão vertical, pode ser responsável pela manutenção do vírus durante várias gerações de uma mesma família[5,6].

A escassez de dados acerca do número de indivíduos infectados pelo aleitamento dificulta o desenvolvimento e implementação de políticas públicas de saúde. Em 2014, por exemplo, foram diagnosticados 72 casos de infecção por HIV em crianças menores de 5 anos[7]. Entretanto, em relação a infecção por HTLV, este número é desconhecido. O objetivo do presente trabalho é estimar o número de casos de infecção por HTLV que ocorrem devido a transmissão vertical no Brasil, anualmente.

METODOLOGIA

Para atingir o objetivo do trabalho e estimar o número de indivíduos infectados por via vertical no Brasil por ano, as seguintes variáveis foram obtidas na literatura e consideradas:

- Número de nascidos vivos no Brasil
- Prevalência da infecção por HTLV-1 em gestantes no Brasil

Submitted 03/23/2017, accepted for publication 09/06/2017 and published 09/29/2017
DOI: 10.17267/2317-3386bjmhh.v5i3.1341

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• Risco de transmissão pelo aleitamento
• Taxa de aleitamento materno dentre as brasileiras de acordo com o período de aleitamento

O risco de desenvolver HAM/TSP e ATL também foi utilizado para calcular o número de casos previstos destas alterações clínicas, a partir do número de casos de infecção por transmissão vertical.

Foram utilizados como referência, os dados disponibilizados pelo Ministério da Saúde do Brasil e os dados obtidos por revisão de literatura na plataforma de artigos científicos PubMed.

RESULTADOS

Para determinar a quantidade de indivíduos que seriam infectados por via vertical no Brasil por ano, considerou-se o número de nascidos vivos no Brasil no ano de 2014 (2.979.259), dados do Ministério da Saúde. De acordo com trabalhos previos, a prevalência da infecção por HTLV-1 em gestantes no Brasil varia entre 0,1-1,1%[1,8–12]. Assim, foram utilizados na análise, diferentes cenários, considerando a maior e menor taxa de prevalência já observada. Logo, estima-se que de 2.929 a 30.757 gestantes encontram-se infectadas com o vírus anualmente. Sabendo que o risco de transmissão vertical depende do período de aleitamento, avaliou-se o número destas mulheres que amamentam até os 6 meses e aquelas que amamentam menos que 6 meses, para, a partir destes dados estimar quantos indivíduos são infectados por via vertical por ano no Brasil.

Assim, sabe-se que 77,6% das brasileiras amamentam os filhos aos 6 meses e 84,6% encontram-se amamentando aos 4 meses após o parto[13]. Extrapolando estes dados para o número de gestantes infectadas de acordo com a menor e maior prevalência observada, teríamos 2.273-23.867 mulheres infectadas amamentando aos 6 meses e 205-2.153 mulheres infectadas por HTLV amamentando que param de amamentar antes de 6 meses. Sabendo que o risco de transmissão pelo aleitamento quando este tem duração menor que 6 meses é de 3,9% e quando superior a este período aumenta para 20,3%[14], estima-se um total de 469 – 4.929 novos casos de infecção vertical por HTLV-1 por ano no Brasil. Aproximadamente 2,5% de transmissão vertical ocorre, independente de ocorrer aleitamento materno[14]. Assim, 73-769 novos casos de infecção são estimados por ano que não poderiam ser evitados com o uso de substituto de leite materno. Além disso, sabendo que cerca de 4% dos indivíduos infectados irão apresentar ATL e 1% irá desenvolver HAM/TSP, estima-se que irão ocorrer, no futuro, cerca de 18-197 novos casos de ATL e 4-49 casos de HAM/TSP em decorrência da transmissão vertical do vírus.

DISCUSSÃO

A infecção pelo HTLV e as doenças associadas permanecem negligenciadas[15]. Enquanto a ATL está associada a elevada letalidade e baixa sobrevida, a HAM/TSP é uma doença crônica, incapacitante com acentuada queda na qualidade de vida. Não há cura, apenas manejo dos sintomas, onerando o sistema de saúde e causando impacto negativo na vida dos portadores. Assim, a prevenção é o melhor modo de abordar a enfermidade. Para a implementação de medidas efetivas de controle de disseminação deste vírus é necessário o conhecimento da realidade de cada localidade. Conhecer o número de novos casos por ano que ocorrem por transmissão vertical no Brasil é essencial e pode servir como norteador para o desenvolvimento e implementação de políticas públicas de saúde que visem o controle desta infecção.

No presente estudo estimamos que ocorra um grande número de casos novos de infecção pelo HTLV-1 por transmissão vertical a cada ano no Brasil (469 a 4.929). Ao comparar com outras doenças que atualmente estão inseridas na testagem pré-natal e neonatal, como HIV, este dado se torna mais evidente.

Além disso, ressalta-se que a realização da testagem no pré-natal e posterior uso de substitutivo de leite materno seria capaz de prevenir, no futuro, cerca de 18-197 novos casos de ATL e 4-49 casos de HAM/TSP em decorrência da transmissão vertical do vírus a cada ano. Estas doenças apresentam elevada morbidade e mortalidade. No entanto, mesmo a infecção assintomática, acarreta grande impacto negativo na vida dos portadores do HTLV. Já foi

demonstrado diminuição na qualidade de vida, aumento de incidência de depressão e ansiedade dentre os carreadores assintomáticos[16,17].

Outro aspecto relevante é que neste estudo podemos estar subestimando o número de casos de indivíduos que irão desenvolver manifestações clínicas decorrentes da infecção pelo HTLV. Apesar de utilizarmos os percentuais descritos na literatura, estudos recentes já indicam que no Brasil podemos ter maior percentual de HAM/TSP e de outras doenças neurológicas dentre os indivíduos infectados, uma vez que não existe notificação compulsória da infecção e complicações.[18] No estudo de Tanajura e colaboradores, observou-se incidência elevada de alterações neurológicas ao acompanhar uma coorte de indivíduos assintomáticos durante 8 anos.

Destaca-se que a inserção da testagem no pré-natal também preveniria a transmissão vertical pelo HTLV-2. Este tipo viral não foi incluído no estudo pois os dados acerca da prevalência do mesmo no Brasil são extremamente escassos, principalmente em gestantes.

Ressalta-se ainda, que impedindo o surgimento de um único caso novo, é possível inibir a cadeia de transmissão desse indivíduo, bloqueando a manutenção do vírus durante gerações e disseminação intra-familiar (por exemplo: transmissão do pai para a mãe, da mãe para os filhos; dos filhos para as esposas, etc..), fato comumente observado na infecção pelo HTLV[5,6].

Por fim, este estudo demostrou que a não implementação do teste na rotina dos exames realizados no pré-natal pelo SUS não pode ser justificado pela escassez de indivíduos infectados, uma vez que no programa nacional de triagem neonatal estão incluídos testes como, por exemplo, fibrose cística que acomete cerca de 1.250 brasileiros e fenilcetonúria que acomete 1.225 habitantes no Brasil[19,20].

Assim, a testagem para HTLV-1/2 deve ser implementada como exame de rotina no acompanhemento pré natal oferecido pelo SUS, de forma que se assegure o que estabelece a Constituição brasileira: a saúde como direito universal.

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APLICAÇÃO DE ESCALA DE INCAPACIDADE NEUROLÓGICA ESPECÍFICA EM PORTADORES DE HTLV-1 DE ACORDO COM O GRAU DE ENVOLVIMENTO NEUROLÓGICO

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INTRODUÇÃO

O vírus T-linfotrópico humano 1 (HTLV-1) é um Deltaretrovirus que está associado à Paraparesia Espástica Tropical/Mielopatia Associada ao HTLV-1 (HAM/TSP), uma doença caracterizada por evolução lenta e progressiva, que pode levar a uma síndrome medular com manifestações no controle motor[1].

A alta prevalência da infecção por HTLV na Região Amazônica tem colocado em destaque o estado do Pará, que ocupa o terceiro lugar no ranking em número de casos entre 7,8 doadores de sangue do Brasil[2,3]. Estudos soroepidemiológicos e moleculares direcionados para comunidades com populações específicas em nível regional registraram prevalência de 1,8% para HTLV-1, entre 168 imigrantes japoneses residentes no município de Tomé-Açú (PA)[4], variação de zero a 2,06% em comunidades remanescentes de quilombolas, na Ilha do Marajó-PA[5] e, em um estudo de base populacional rural realizado em comunidades ribeirinhas de fácil acesso à Belém, foi encontrada uma prevalência encontrada para o HTLV-1 de 1,14%[6].

Embora boa parte dos indivíduos portadores do vírus permaneça assintomática ao longo da vida, múltiplos aspectos sobre evolução, perfil da incapacidade e opções terapêuticas continuam sendo obscuros pela inexistência de uma ferramenta adequada de mensuração de saúde específica para avaliação do quadro neurológico associado ao HTLV-1. Diante disso, a Escala de Incapacidade Neurológica do Instituto de Pesquisa Clínica Evandro Chagas-2 (EIPEC-2) foi um instrumento desenvolvido exclusivamente para avaliação de pacientes com HAM/TSP, porém ainda não validado[7,8].

Sendo assim, o objetivo deste trabalho foi descrever os resultados da aplicação da escala EIPEC-2 e as características epidemiológicas em portadores de HTLV-1 atendidos no ambulatório do Núcleo de Medicina Tropical da Universidade Federal do Pará.

MATERIAL E MÉTODOS

Estudo de corte transversal com 39 pacientes encaminhados por unidades de saúde de referência, advindos por demanda espontânea, ou convidados via telefônica a partir do banco de dados do Ambulatório do Núcleo de Medicina Tropical (NMT) da Universidade

Submitted 03/23/2017, accepted for publication 09/06/2017 and published 09/29/2017
DOI: 10.17267/2317-3386bjmhh.v5i3.1341

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Federal do Pará (UFPA), entre o período de março a junho de 2017. Os pacientes com sorologia indeterminada foram excluídos da nossa amostragem.

Em todos os casos, o diagnóstico laboratorial foi estabelecido pela detecção de anticorpos pelo método de ensaio imunoenzimático para a detecção de anticorpos anti-HTLV (ELISA - Ortho Diagnostic System Inc., NJ, EUA e Chiron Emeryville, CA, EUA), de acordo com instruções do fabricante. As amostras com resultados reagentes e com valores próximos aos do cutoff, foram testadas em duplicata e, as amostras consideradas positivas pelo ELISA, foram analisadas pela técnica de reação em cadeia da polimerase (PCR), seguida da utilização da enzima Taq I na digestão enzimática, uma endonuclease de restrição, que diferencia os HTLV dos tipo 1 e 2. A técnica emprega a detecção do DNA proviral pela amplificação da região pX do vírus. Além disso os pacientes foram avaliados usando um inquérito clínico-epidemiológico padronizado para determinar as manifestações iniciais da infecção pelo HTLV-1 e submetidos a uma completa avaliação clínica e neurológica para diagnóstico de HAM/TSP.

A Escala de Incapacidade Neurológica do Instituto de Pesquisa Clínica Evandro Chagas-2 (EIPEC-2) foi o instrumento utilizado para avaliação de pacientes. Ela abrange faixas de pontuação total variando de 0 a 29, com 17 pontos possíveis para o escore motor, 3 para espasticidade, 4 para avaliação sensorial e 5 para pontuação dos esfíncteres, sendo um maior quantitativo de pontos indicativo de incapacidade neurológica mais severa. Além disso, utiliza dados mais objetivos, menos sujeitos a interpretações do paciente e mais à própria observação do profissional que a aplica.

Os pacientes foram divididos em três grupos por ordem decrescente de envolvimento neurológico, segundo proposta atualizada dos critérios de diagnóstico clínico para HAM/TSP10 conforme disposto a seguir:

• O 1° grupo denominado "Definitivo" tendo como seguintes critérios: 1.Paraparesia espástica progressiva não remissiva com marcha suficientemente prejudicada percebida pelo paciente. Sinais e sintomas sensoriais podem ou não estar presentes. Quando presentes permanecem sutis e sem um nível sensório definido. Sinais e sintomas esfincteriano urinário e anal podem ou não estar presente; 2.Presença de anticorpos contra o HTLV-1 em soro e líquido cefalorraquidiano (LCR) confirmado por Western Blot e/ou um PCR positivo para HTLV-1 em sangue e/ou LCR.; 3.Exclusão de outras doenças que lembrem HAM/TS);
• O 2° grupo chamado "Provável" com: 1. Apresentação monosintomática: espasticidade ou hiperreflexia em membros inferiores ou sinal de Babinski isoladamente com ou sem sinais e sintomas sensórios sutis, ou bexiga neurogênica somente confirmada por teste urodinâmico; 2.Presença de anticorpos contra o HTLV-1 em soro e/ou LCR confirmado por Western Blot e/ou um PCR positivo para HTLV-1 em sangue e/ou LCR; 3.Exclusão de outras doenças que lembrem HAM/TSP;
• O 3° grupo dito "Possível" com: 1. Apresentação clínica completa ou incompleta; 2.Presença de anticorpos do HTLV-1 em soro e/ou LCR confirmado por Western Blot e/ ou um PCR positivo para HTLV-1 em sangue e/ou LCR; 3.Doenças que lembram HAM/TSP sem serem excluídas.

Todos participantes preencheram consentimento informado e o estudo foi aprovado pelo comitê de ética em pesquisa do Núcleo de Medicina Tropical da Universidade Federal do Pará sob o parecer n° 1.898.095/2017.

Os resultados foram processados através de recursos da estatística descritiva mediante utilização do programa Excel (Microsoft for Windows – 2010). Médias e desvios padrões foram calculados para as variáveis demográficas de todos pacientes, sendo utilizado o teste de ANOVA para comparação entre médias e, caso havendo significância estatística, foi utilizado o pós-teste de Tukey a fim de discriminar em qual(is) grupo(s) estariam às diferenças. O teste do Qui-quadrado foi utilizado para comparação entre percentuais. Foi considerado como significante o valor de $p \leq 0,05$ ($\alpha = 5\%$).

RESULTADOS

Houve predomínio no estudo de 74,4% do sexo feminino com média de 52 anos de idade (DP±13,2), porém, sem diferença estatística (p=0,366), quando comparado ao grupo masculino (56,3±8,3 anos

de idade). Quanto à procedência 61,54% eram da cidade de Belém-PA. Em relação ao estado civil 51,28% eram casados, e quanto à renda familiar, 84,63% possuíam entre 1 e 4 salários, sendo que 2,6% tinham renda inferior a 1 salário mínimo.

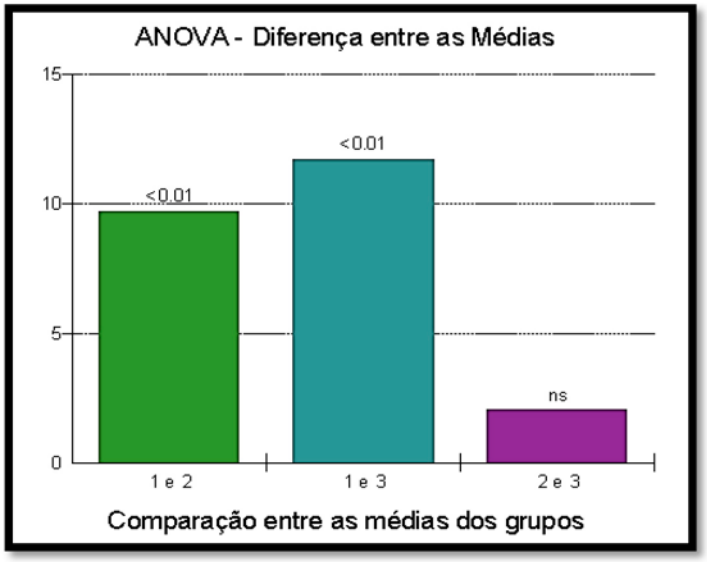
Os aspectos demográficos e clínicos dos participantes do estudo agrupados de acordo com o grande envolvimento neurológico são mostrados na Tabela 1. A média de idade foi maior no grupo 3, porém sem diferença estatisticamente significante quando comparado com outros grupos. Houve também maior prevalência de mulheres no grupo 3 em relação aos demais grupos, mas sem diferença significante. A maioria dos pacientes foi procedente de Belém (61,64%), concordando com o grupo com mielopatia que teve maior percentual de pessoas procedentes da capital (38,46%). Os Grupos 1, 2 e 3 apresentaram respectivamente as seguintes pontuações na EIPEC-2: 16,3±5,3; 6,6±4,1; 4,6±3,7.

Tabela 1. Aspectos demográficos e clínicos de indivíduos portadores de HTL divididos por grupos de acordo com o grau de envlvimento neurológico. Belém-PA, 2017.

	Grupo 1 Definitivos (n=13)	Grupo 2 Prováveis (n=10)	Grupo 3 Possíveis (n=16)	p
Idade	52,8±7,9	51,4±14,5	54,4±14,0	0,83[a]
Gênero				
Masculino	04 (30,7%)	03 (30%)	03 (18,7%)	0,71[b]
Feminino	09 (69,3%)	07 (70%)	13 (81,3%)	
Estado Civil				
Casados	06 (46,2%)	04 (40%)	10 (62,5%)	0,48[b]
Não casados	07 (53,8%)	06 (60%)	06 (37,5%)	
Procedência				
Belém	08 (61,5%)	09 (90%)	10 (43,7%)	0,06[b]
Outras cidades	05 (38,5%)	01 (10%)	06 (56,3%)	
Renda Familiar				
< 1 salário	0	01 (10%)	0	0,54[b]
Entre 1 e 4 salários	11 (84,6%)	08 (80%)	14 (87,5%)	
> 4 salários	02 (15,4%)	01 (10%)	02 (12,5%)	

Na Figura I, observa-se a comparação das médias de pontuação da EIPEC-2 nos grupos estudados. Pode-se notar diferença estatística entre Grupo 1 vs Grupo 2 e entre Grupo 1 vs Grupo 3 ($p<0,01$).

Figura I. Comparação das médias de pontuação da EIPEC-2 entre os grupos estudados.
Grupo 1: Definidos (n=13); Grupo 2: Prováveis (n=10); Grupo 3: Possíveis (n=16), Belém-PA, 2017.



Quanto à subseção da marcha no escore motor da EIPEC-2, o Grupo 1 apresentou 30,77% em necessidade de apoio para caminhar e 69,23% em uso de cadeira de rodas como dispositivo para locomoção. Tanto o Grupo 2 quanto o Grupo 3 apresentaram uma faixa reduzida de indivíduos que precisam de apoio para deambulação (10% e 6,25% respec--tivamente), sendo os demais independentes para marcha.

DISCUSSÃO

A detecção precoce de incapacidades funcionais neurológicas, bem como a classificação do grau de comprometimento, é essencial para o acompanhamento e a intervenção clínica adequada. A utilização de escalas de incapacidade neurológica facilita a determinação do estágio clínico, bem como uniformiza a avaliação de resposta à terapêutica[11].

Estudos tem demostrado que a EIPEC-2 apresenta melhor desempenho geral do que todas as outras escalas consideradas, habitualmente utilizadas para avaliação de incapacidade neurológica na MAH/ PET, disponíveis na literatura[9,12]. Além disso, esta ferramenta tem apontado melhora na qualidade assistencial no atendimento de indivíduos com HAM/TSP que permite investigar, com observação mais precisa o grau de incapacidade e a resposta às intervenções terapêuticas. Logo, torna-se importante na realização de ensaios clínicos, a uniformização das informações assim como um instrumento de mensuração objetivo e preciso. Além disso, muito poderá ser elucidado sobre a história natural da HAM/TSP, o perfil de incapacidade da população acometida e o impacto desta doença nas populações estudadas[9].

No presente estudo houve predomínio de 74,4% do sexo feminino com média de 52 anos de idade (DP±13,2). O dado encontrado foi ao encontro com os achados de um estudo realizado no Instituto de Pesquisa Clínica Evandro Chagas (IPEC), FIOCRUZ, Rio de Janeiro, no qual avaliou a influência do gênero na progressão clínica da HAM/TSP[7].

Em outra pesquisa realizada no Reino Unido em 2012, no qual testou se a inibição da ativação das células T com a ciclosporina A seria segura e benéfica em pacientes com HAM / TSP inicial e/ou clinicamente progredindo, os valores apresentados pela EIPEC-2 também foram similares ao grupo 1 do presente estudo (14,5)[8].

Sendo assim, a avaliação da incapacidade funcional neurológica pela EIPEC-2 demonstrou coerência na pontuação dos escores de acordo com o grau de envolvimento neurológico de cada grupo avaliado. Portanto, sugere-se o uso desta escala específica pela necessidade de uma mensuração precoce da HAM/TSP.

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POLIMORFISMOS DE IFNG +874A/T ENTRE PESSOAS ASSINTOMÁTICAS INFECTADAS PELO HTLV-1, ESTÃO RELACIONADOS AO PIOR PROGNÓSTICO E O DESENVOLVIMENTO DE DOENÇA

IFNG +874A/T POLYMORPHISM AMONG HTLV-1 INFECTED ASYMPTOMATIC PERSONS IS RELATED WITH A WORST PROGNOSIS AND DISEASE DEVELOPMENT

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INTRODUÇÃO

A infecção pelo HTLV-1 está distribuída mundialmente, com aproximadamente 10 milhões de pessoas infectadas de forma endêmica no Japão, África subsaariana, América Latina, Caribe, Oriente Médio, Região da Austro-Melanésia e América do Sul. O Brasil representa uma importante área endêmica para o vírus com grande diversidade de doenças associadas ao HTLV-1, sendo que a prevalência da infecção varia entre as diferentes regiões do país e a região sul apresenta as menores taxas e a região nordeste, as mais elevadas[6].

A maioria das infecções é assintomática, entretanto, em certas condições, ainda não totalmente compreendidas, a infeção pelo vírus pode causar o desenvolvimento de quadros clínicos que incluem a Paraparesia Espástica Tropical/Mielopatia associada ao HTLV-1 (PET/MAH), Leucemia/Linfoma de Células T do Adulto (LLcTA) e síndromes inflamatórias como artrite reumatoide, dermatite e uveíte[15]. Vários estudos têm investigados fatores da resposta imunológica, que possam esclarecer o curso da infecção pelo HTLV-1[3,5,7,11].

A infecção pelo HTLV-1 induz proliferação espontânea de linfócitos T CD4+, CD8+ e células NK[13]. O aumento do número destas células pode levar o desenvolvimento de linfócitos autoreativos e a secreção acentuada de citocinas pró-inflamatórias, como IFN-γ, que podem contribuir para a patogênese das desordens inflamatórias associadas ao HTLV-1[20].

O gene IFNG apresenta uma sequência microssatélite de repetições CA, no primeiro intron do gene, que é polimórfica e, um dos principais polimorfismos localizados nessa região, o IFNG +874 A/T, corresponde a uma transição de adenina (A) para timina (T), estando relacionado com a produção variada de IFN-γ[14]. A presença deste polimorfismo tem sido associada com infecções virais, incluindo o HIV-1, o vírus da hepatite B e o citomegalovírus[2,8,19].

Considerando que indivíduos sintomáticos para doenças relacionadas ao HTLV-1 apresentam uma resposta inflamatória acentuada, o presente trabalho teve como objetivo investigar a influência do polimorfismo IFNG +874 A/T nos níveis plasmáticos da citocina IFN-γ e sua relação na progressão da infecção à doença.

Submitted 03/23/2017, accepted for publication 09/06/2017 and published 09/29/2017
DOI: 10.17267/2317-3386bjmhh.v5i3.1341

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MATERIAIS E MÉTODOS

População do estudo. O presente estudo incluiu amostras de sangue de 153 indivíduos infectados com HTLV-1 (33 clinicamente diagnosticados como PET/MAH, 22 com manifestações reumatológicas, 2 com dermatite, 1 com uveíte e 95 pessoas assintomáticas) de ambos os sexos, com idade superior a 18 anos, sem terapia antirretroviral e/ou tratamento com glucocorticóides, atendidos no ambulatório do Núcleo de Medicina Tropical da Universidade Federal do Pará.

Extração de DNA. O DNA foi extraído de leucócitos do sangue periférico usando o kit Puregene (Puregene, Gentra Systems, Inc., EUA) conforme o protocolo do fabricante, que incluiu os passos da lise celular, precipitação de proteínas, precipitação e hidratação do DNA.

Após a extração, o DNA obtido foi quantificado usando o aparelho Qubit® 2.0 Fluorometer (Life Technologies, Carlsbad, California, USA) e reagentes do Qubit™ DNA Assay Kit (Life Technologies, Carlsbad, California, USA) seguindo o protocolo recomendado pelo fabricante.

Quantificação da carga proviral HTLV. A carga proviral foi quantificada por qPCR usando três sequências alvos, sintetizada através do sitema TaqMan® (Life Technologies, Foster City, CA, USA), de acordo com protocolo previamente descrito[17].

Genotipagem de IFN-γ +874 A/T (rs2430561). A análise do polimorfismo IFNG +874 A/T localizado no primeiro intron do gene que codifica a citocina IFN-γ foi realizada pela técnica de PCR em tempo real, por meio do aparelho StepOnePLUS™Real-Time PCR System. Foram utilizadas sequências específicas de iniciadores (IFNG-F: 5'-TTC AGA CAT TCA CAA TTG ATT TTA TTC T-3 e IFNG-R: 5'-CCC CCA ATG GTA CAG GTT TC-3') e a sondas (FAM-AAAA-TCAAATCTCACACACACA-MGB e VIC-AAAATCAA-ATCACACACACACA-MGB), descritas anteriormente[18]. A reação iniciou com a manutenção da amostra por 10 minutos a 95°C e 40 ciclos de 15 segundos a 95°C e 1 minuto a 60°C.

Dosagem do IFN-γ plasmático. A concentração do IFN-γ plasmático foi mensurada por meio do teste imunoenzimático do tipo ELISA (Human ELISAReady-SET-Go, EBioscience, Inc. California, San Diego, USA). Este método utiliza anticorpos monoclonais específicos para detectar a citocina e foi realizado de acordo com as instruções recomendadas pelo fabricante (Human MBL Quantikine ELISA Kit, R & D system, USA).

Análise Estatística. As frequências genotípicas e alélicas foram estimadas por meio de contagem direta e a significância das diferenças entre os grupos estudados foi calculada utilizando o teste $\chi 2$ (qui-quadrado). O cálculo do equilíbrio de Hardy-Weinberg foi realizado para avaliar se as distribuições das frequências genotípicas observadas estavam de acordo com o esperado. A avaliação dos níveis plasmáticos de IFN-γ entre os grupos investigados foi realizada por meio do teste não paramétrico Mann-Whitney. Todos os testes foram realizados utilizando-se o programa BioEstat 5.34, sendo consideradas associações significantes aquelas com valor de $p<0,05$.

Aspectos Éticos. O projeto foi aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário João de Barros Barreto da Universidade Federal do Pará (protocolo nº 2061/2005).

RESULTADOS

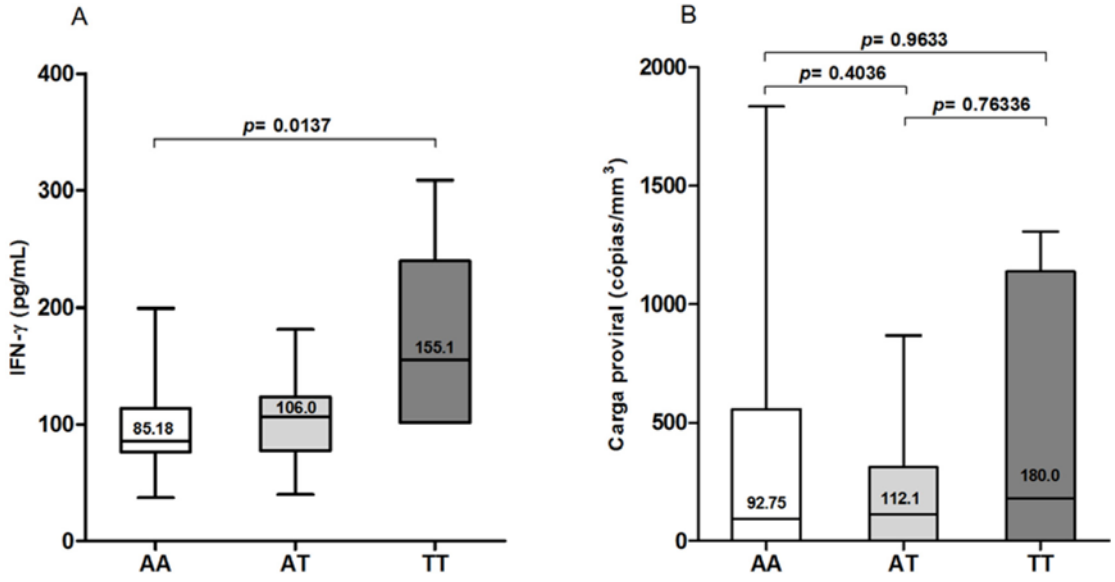
A frequência do genótipo selvagem foi maior em ambos os grupos, mas não foi observada diferença estatística significativa entre os genótipos do grupo de indivíduos assintomáticos quando comparados com os indivíduos que apresentaram sintomas relacionados ao HTLV-1. No entanto, a presença do alelo T foi significativamente maior ($p<0,0142$) entre os assintomáticos (Tabela 1). Os níveis plasmáticos de IFN-γ foram significativamente mais elevados ($p<0,0137$) entre o grupo de portadores do genótipo TT, os quais também apresentaram carga proviral mais elevada, porém sem significância estatística (Figura 1).

Tabela 1. Frequência genotípica e alélica para o polimorfismo IFNG +874/T entre indivíduos sintomáticos a assintomáticos infectados pelo HTLV-1.

Genótipos e alelos	Sintomático (n/%)	Assintomático (n/%)	p (χ^2)
AA	34 (58.63)	49 (51.58)	0.6689
AT	19 (32.75)	39 (41.05)	
TT	5 (8.62)	7 (7.37)	
*A	0.87	0.72	0.0142
*T	0.13	0.28	

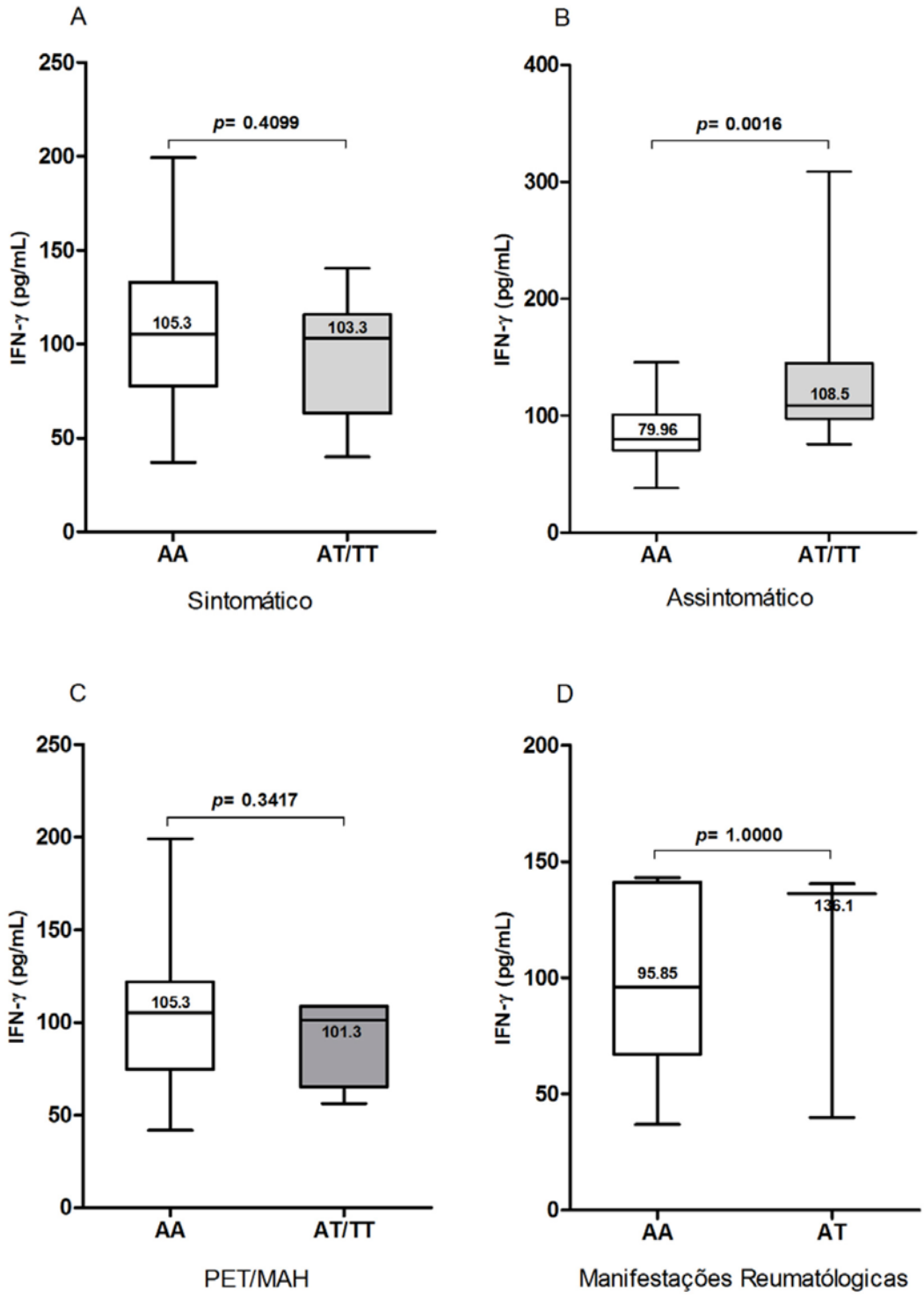
n= número de indivíduos; χ^2: teste qui-quadrado.

Figura 1. (A) Níveis plasmáticos de IFN-γ e (B) carga proviral entre indivíduos portadores dos genótipos de IFNG +874A/T infectados pelo HTLV-1. Teste Mann Whitney test.



Os níveis plasmáticos de IFN-γ na infecção pelo HTLV-1 entre os grupos sintomáticos e assintomáticos, mostrou uma diferença não significativa no grupo de doentes (Figura 2A), mesmo quando a avaliação foi feita de acordo com doenças relacionadas (TSP/HAM ou doença reumatológica; Figura 2C e 2D). Entretanto, a diferença dos níveis de IFN-γ entre os indivíduos assintomáticos, foi significativamente maior ($p<0,0016$) entre àqueles que apresentaram o alelo T, cujos níveis foram semelhantes aos dos pacientes sintomáticos (Figura 2B).

Figura 2. Níveis plasmáticos de IFN-γ entre indivíduos (A) sintomáticos, (B) assintomáticos portadores dos genótipos de IFNG +874A/T infectados pelo HTLV-1 e (C, D) de acordo com a apresentação de sintomas. Mann Whitney test.



DISCUSSÃO

A resposta imunológica de indivíduos infectados pelo HTLV-1 parece ser modulada pela ação do vírus, podendo promover a proliferação espontânea de linfócitos T CD4+ e CD8+ e acentuar a produção de citocinas pró-inflamatórias, responsáveis pelos sintomas das doenças relacionadas a infecção, principalmente a PET/MAH[10]. Dentre as diversas citocinas envolvidas nesse processo, IFN-γ parece ser a mais importante para a patogênese PET/MAH[12] e, alterações genéticas no gene da citocina poderiam acentuar o processo inflamatório e a gravidade da doença.

No presente trabalho observamos que a frequência do genótipo polimórfico IFNG +874 A/T não foi associada com a presença de sintomas relacionados a infecção pelo HTLV-1, entretanto, foi encontrada maior frequência alélica do polimorfismo no grupo de indivíduos assintomáticos. O alelo selvagem já foi considerado um fator de risco para a infecção pelo HIV-1[8] e para a progressão da hepatite B[2]. Desta forma, o resultado da frequência alélica do polimorfismo, encontrada neste estudo, poderia indicar que o alelo T seria um fator protetor contra o desenvolvimento de sintomas relacionados ao HTLV-1, no entanto, os resultados da dosagem plasmática de IFN-γ em relação aos genótipos mostraram uma situação diferente.

Os níveis plasmáticos de IFN-γ foram significativamente mais elevados nos indivíduos infectados pelo HTLV-1 portadores do genótipo polimórfico de IFNG +874 A/T, os quais apresentaram carga proviral mais elevada, apesar de não significativa, sugerindo que a presença do polimorfismo pode acentuar o processo inflamatório e a progressão da doença. Níveis elevados de IFN-γ em pacientes com PET/MAH já foram associado com a desordem inflamatória do sistema nervoso central[20].

Na avaliação dos níveis de IFN-γ de acordo com os diferentes genótipos, entre os indivíduos sintomáticos e assintomáticos separadamente, foi observado que o polimorfismo não influenciou significativamente os níveis da citocina, nem quando a avaliação foi feita de acordo com os quadros clínicos apresentados. Os resultados são compatíveis, pois como pacientes com PET/MAH e artrite reumatoide apresentam um acentuado processo inflamatório com comprometimento do tecido nervoso e articulações, respectivamente, diversos fatores estão associados à gravidade da doença[1,15] e, deste modo, a presença do polimorfismo IFNG +874 A/T deixa de ser relevante neste contexto.

Em contraste, a análise dos níveis de IFN-γ no grupo assintomático mostrou que indivíduos portadores do alelo polimórfico apresentaram níveis da citocina significativamente mais elevados comparado ao alelo selvagem, demonstrando que para indivíduos infectados pelo HTLV-1 este polimorfismo pode representar um fator de risco para o desenvolvimento dos sintomas relacionados a infecção, uma vez que os mesmos apresentaram níveis de IFN-γ semelhantes aos indivíduos sintomáticos e alguns tiveram carga proviral detectável e, principalmente, porque a elevação do nível de IFN-γ é um marcador imunológico da patogênese de PET/MAH12. Alguns indivíduos assintomáticos infectados pelo HTLV-1 apresentam nível de resposta inflamatória semelhante àqueles com PET/MAH[16]. Nestes indivíduos, a ativação da resposta imune está associada à carga proviral elevada, que pode levar ao desenvolvimento de doenças associadas ao HTLV-1[7].

Em conclusão, os resultados sugerem que o polimorfismo IFNG +874A/T pode influenciar os níveis plasmáticos de IFN-γ na infecção pelo HTLV-1. Indivíduos assintomáticos portadores dos genótipos polimórficos parecem ter maior propensão a desenvolver um processo inflamatório de forma mais rápida, o que poderia facilitar o surgimento de doenças relacionadas ao HTLV-1. A importância dessa descrição se torna ainda mais relevante para que as pessoas portadoras do polimorfismo passem a ter um acompanhamento mais frequente e constante para a avaliação do surgimento dos diversos quadros clínicos associados ao HTLV-1 e o controle da progressão da doença.

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