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ORIGINAL ARTICLE

Rate of positive autoimmune markers in Human T lymphotropic virus type 1 carriers: a case-control study from Iran

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Abstract

Aim: Human T lymphotropic virus type 1 (HTLV-1) infection with high prevalence in the north-east of Iran, particularly in Mashhad, can lead to adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and a variety of autoimmune diseases. The aim of the study was to examine the presence of autoimmune markers in HTLV carries.

Methods: Serum samples were obtained from blood donors in Mashhad, northeastern Iran. One hundred and five HTLV-1 positive (cases) and 104 age- and sex-matched HTLV-1 negative donors (controls) were assessed for presence of serum autoimmune markers by enzyme-linked immunosorbent assay.

Results: The mean ages of cases and controls were 40.8 ± 9.4 and 41.5 ± 9.3 years, respectively ($P = 0.5$). In the case group, 81.9% and in the control group 83.7% were male ($P = 0.74$). The frequency of positive antinuclear antibodies and anticyclic citrullinated peptide antibodies in the serum of the two groups were not significantly different ($P = 0.68$ and $P = 0.62$, respectively). Only one antineutrophil cytoplasmic antibody-positive case (1%) was observed in the group and no anti-phospholipid immunoglobulin G positivity was observed. The frequency of rheumatoid factor (RF) was greater in case group than in the control group, although the difference was not significant ($P = 0.08$). The amount of RF in all 12 RF positive sera were higher than normal levels (33–37 IU/mL).

Conclusion: Because we failed to detect any significant relation between serum autoimmune markers and HTLV-1 infection, and because of the relatively low prevalence of autoimmune diseases, it could be concluded that healthy HTLV-1 carriers do not produce rheumatologic-related auto-antibodies more than the healthy population.

Key words: autoimmune markers, autoimmunity, case-control study, Human T lymphotropic virus type 1, HTLV-1, HTLV1, Iran.

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INTRODUCTION

Viruses, especially retroviruses, have been repeatedly discussed as etiologic agents of autoimmune and rheumatic disorders; however, the certain role of viruses in

development of these diseases remains unclear. Retroviruses could infect immune cells and have therefore been suggested as potential activating agents in autoimmune diseases.[1]

Infection with human T lymphotropic virus type 1 (HTLV-1), as the first identified human retrovirus,[2] is a worldwide health problem and approximately 15–20 million persons are estimated to be infected with the virus.[3] The infection occurs predominantly in Africa, South America, the Caribbean basin and southwest Japan.[3] Furthermore, high rates of HTLV-1 seroprevalence in the general population or specific groups have been reported from northeastern Iran. In our previous study in the general population, the rate of HTLV-1 infection in Mashhad city was reported as 2.12%.[4]

The pathogenesis of HTLV-1 infection is not completely understood; both T cell activation and proviral load determine the infection outcomes. Although the majority of HTLV-1 carriers remain asymptomatic in their lifetime, the virus is associated with two major diseases, adult T cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[5] In addition, several studies have showed that symptoms of some other inflammatory and autoimmune disorders are more common in HTLV-I-infected individuals.[6,7]

Several studies on HTLV-1 infection prevalence in patients with autoimmune diseases such as lupus erythematosus,[8] Hashimoto's thyroiditis,[9] Sjögren's syndrome,[10] rheumatoid arthritis,[11] polymyositis[12] and antiphospholipid syndrome[13] around the world have been reported. Further, some data have shown other autoimmune manifestations of HTLV-1 infection, such as uveitis,[14] sensory polyneuropathy,[15] interstitial lung disease[16] and infective dermatitis.[17] HTLV-1 has been implicated in chronic joint inflammation and proviral DNA has been detected in both synovial fluid and synovial cells.[18] Since HTLV-1 virus interferes with T regulatory cell activities, which release antigens from cells destroyed by the virus, it could lead to antigen cross-reactivity between viral antigens and autoantigens. Autoimmune diseases are characterized largely by the presence of autoantibodies. Evaluating autoantibodies in HTLV-1 infected patients could be helpful in various fields of pathogenesis and etiology of autoimmune diseases in this population.[19,20]

Despite a considerable amount of indirect evidence that retroviruses might indeed be involved in triggering or perpetuating autoimmune rheumatic diseases, direct evidence about autoantibody formation is still missing. Autoimmune marker seropositivity has not been determined in healthy HTLV-1 carriers from the northeast of Iran, an endemic area of the infection. In this study we tried to find if healthy HTLV-1 carriers show a higher rate of seropositivity for some rheumatologic autoantibodies, including antinuclear antibody (ANA) and ANA profile, anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF), and anti-phospholipid immunoglobulin G (IgG) and anti-cyclic citrullinated peptide (anti-CCP) antibodies in comparison with individuals who showed no serologic evidence of this virus.

MATERIALS AND METHODS

Study population

This cross-sectional case-control study was conducted participants from June to September 2014 in Mashhad, northeastern Iran. One hundred and five HTLV-1 positive (cases) and 104 age- and sex-matched HTLV-1 negative donors (controls) were assessed for presence of serum autoimmune markers. None of the cases or controls showed a neurologic manifestation of HTLV-1 infection, nor signs and symptoms of rheumatic diseases in medical evaluation by trained physicians in the blood centers.

This study was approved by the ethics committee of Mashhad University of Medical Sciences (No: 7232) and the Research and Technology Deputy of the Academic Center for Education, Culture and Research (ACECR) (No: 2–2100).

Serological assays

Serum samples were routinely screened for HTLV antibodies against HTLV-1 p19, gp21, gp46 and HTLV-2 gp21 and gp46 by enzyme-linked immunosorbent assay (ELISA, Adaltis S.r.l., Guidonia Montecelio, Italy) according to the manufacturer's instructions. Western blot technique (MP Diagnostics HTLV Blot 2.4, MP Biomedicals Asia Pacific Pte Ltd, Singapore, Singapore) was carried out in the blood centers for all positive ELISA samples for further confirmation of the infection, according to the manufacturer's instructions. All sera were also tested for the presence of autoantibodies by ELISA kits in the Central Medical Laboratory of ACECR, Mashhad Branch. These included: ANA, ANCA, anti-CCP and anti-phospholipid IgG antibodies (AESKU.DIAGNOSTICS, Wendelsheim, Germany). According to the manufacturer's instructions, the samples were considered seropositive if the sample's optical density (OD) was more than 1.2 OD of the cut-off. The sera within a range of 20% around

the cut-off were considered as equivocal and the test was repeated by the same protocol. Moreover, a quantitative test was used to determine RF (Bionik, Tehran, Iran); the values up to 20 IU/mL were considered as normal levels.

The ANA reactive serum samples were rechecked for IgG antibodies against eight cellular and nuclear antigens (ANA profile) including Smith antigen (Sm), U1 small nuclear ribonucleoprotein (U1 snRNP), snRNP/Sm proteins, anti-Sjögren's-syndrome-related antigen A (SS-A), Sjögren's syndrome antigen B (autoantigen La) (SS-B), anti-topoisomerase I (Scl-70), centromere protein B (CenpB) and histidyl tRNA synthetase (Jo-1) by the ELISA kits (AESKU, Germany). Moreover, perinuclear ANCA (p-ANCA) and cytoplasmic ANCA (c-ANCA) were evaluated in sera with a reactive result for ANCA by the ELISA kits (AESKU, Germany).

Statistical analysis

All statistical analyses were performed using SPSS software (Version 18.0., SPSS Inc., Chicago, IL, USA). Differences in age and sex distributions between HTLV-1 positive and negative blood donors were assessed by *t*-test and Chi-square, respectively. Comparisons of the markers' seropositivity in the two study groups were also performed by Chi-square test. *P*-values < 0.05 were considered statistically significant.

RESULTS

One-hundred and five HTLV-1 seropositive blood donors including 86 men and 19 women and 104 HTLV-1 seronegative volunteers comprising 87 men and 17 women were included. No difference was found between the mean age of cases (40.81 ± 9.37 years) and controls (41.46 ± 9.27 years, $P = 0.5$) and the sex distribution of both groups ($P = 0.7$).

ANA seropositivity was observed in six participants, including four (3.8%) cases and two (1.9%) controls; the difference was not significant between the two groups ($P = 0.68$) (Table 1). All ANA-positive subjects were seronegative for U1-RNP, Sm, SS-B, Scl-70, CenpB and Jo-1. Only one from the case group was seropositive for Sm/RNP and two were positive for SS-B. Furthermore, only one individual HTLV-1 positive person showed reactivity for ANCA; both p-ANCA and c-ANCA markers were not positive for that case. None of the HTLV-1 negative individuals showed ANCA seropositivity. The overall prevalence of anti-CCP seropositivity was 2.9% (3/105) in HTLV-1 positive, and 0.96% (1/104) among negative subjects ($P = 0.62$).

Anti-phospholipid antibodies were not detected in any case of the studied populations. On the other hand, nine (8.6%) of the cases and three (2.9%) controls were seropositive for RF, with no significant difference between the two groups ($P = 0.07$). In all 12 above-mentioned persons, the range varied from 33 to 37 IU/mL (Table 1).

DISCUSSION

Disease progression and ongoing inflammation affecting different organs of the human body are the common features of autoimmune diseases with unknown etiology. This study indicated no difference in autoantibody seropositivity between HTLV-1 positive and HTLV-1 negative individuals. There is no doubt that retroviruses could modify immune reactivity by different mechanisms. Modification of the immune response might be induced by the infection of both

Table 1 Autoimmune marker seropositivity in HTLV-1-positive and negative blood donors

Variable		HTLV-1 positive *n* (%)	HTLV-1 negative *n* (%)	*P*-value
ANA	Positive	2 (1.9%)	2 (1.9%)	0.68†
	Negative	103 (98.1%)	102 (98.1%)	
ANCA	Positive	1 (0.96%)	0	-
	Negative	104 (99/04%)	104 (100%)	
Anti-CCP	Positive	3 (2.9%)	1 (1%)	0.62†
	Negative	102 (97.1%)	103 (99%)	
RF	Positive	9 (8.6%)	3 (2.9%)	0.07‡
	Negative	96 (91.4%)	101 (97.1%)	
Anti-phospholipid IgG	Positive	0	0	-
	Negative	105 (100%)	104 (100%)	

†Fisher exact test, ‡Chi-square test. HTLV-1, human T lymphotropic virus type 1; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-CCP, anti-cyclic citrullinated peptide antibodies; RF, rheumatoid factor; IgG, immunoglobulin G.

lymphopoietic and hematopoietic cells, or by a direct toxic effect of viruses on certain target cells.[21] Immune complex formation of viruses with the corresponding antibodies could lead to the induction of vasculitis, and the persistence of proviruses or viral antigens could be involved in the perpetuation of chronic inflammatory reactions, such as in virus-associated reactive arthritis. Sato *et al.*[18] reported a series of 10 patients with chronic persistent oligoarthritis, affecting mainly the large joints, in association with HTLV-1 infection. Recent studies have further evaluated the pathogenic mechanisms responsible for inflammatory arthritis in association with HTLV-1 infection. Locally expanded T cell clones against various antigens in the joint are considered to play a role in producing arthritis in HTLV-1 env-px transgenic rats.[22] Important findings of some studies on autoantibodies associated with HTLV-1 infection are summarized in Table 2.

Another study in Mashhad[23] found no significant difference in T lymphocyte apoptosis rate in protein levels between lupus patients and healthy control groups. Another survey in the northeast of Iran concluded that HTLV-1 infection was not a predisposing factor for systemic lupus erythematous (SLE).[8] Lack of any

Table 2 Summary of studies discussing relationship between HTLV-1 infection and seropositivity of rheumatologic autoimmune markers

Study	Location/date	Research groups	Autoantibodies studied	Results
Talarmin *et al.*[30]	French Guinea, 1997	1. HTLV-1 carriers 2. HAM/TSP patients	ANA	No significant difference in frequency of ANA seropositivity between both groups
Karine *et al.*[31]	Brazil, 2010	1. KCS with HTLV-1 seropositivity 2. KCS patients without HTLV-1 infection 3. Healthy HTLV-1 carriers	ANA Anti-SSA/Ro Anti-SSB/La RF	No autoantibodies in patients with KCS and HTLV-1 carriers were detected
Wilson *et al.*[32]	USA, 1995	1. HAM/TSP patients	Anti-cardiolipin antibody	Anti-cardiolipin antibody was positive in 26% of HAM/TSP patients
Ohishi *et al.*[28]	Japan, 1996	1.HTLV-1 carriers 2. Healthy individuals	ANA Anti-SSA/Ro Anti-SSB/La Anti-thyroglobin antibody (anti-Tg)	RF and anti-Tg in HTLV-1 carriers were higher than those in healthy individuals, but lower levels of ANA were detected in this group.
Gilbert *et al.*[33]	Jamaica, 2001	1. Polymyositis patients with HTLV-1 infection 2. Polymyositis patients without HTLV-1 infection	ANA Anti-Jo-1	A significant relation between ANA and anti-Jo-1 levels was not seen in both groups.
Nakamura *et al.*[11]	Jamaica, 2000	1. HTLV-1 carriers with Sjögren patients 2. HAM/TSP patients with Sjögren 3. Sjogren patients without HTLV-1	ANA Anti-SSA/Ro Anti-SSB/La	Frequency of autoantibodies was not significantly different in three groups.
Current study		1. Healthy HTLV-1 carriers 2. Individuals without HTLV-1 infection	ANA Anti-cardiolipin RF ANCA Anti-CCP	Frequencies of autoantibodies studied in two groups were not significantly different

KCS, kerato-conjunctivitis sicca; HTLV-1, human T lymphotropic virus type 1; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-CCP, anti-cyclic citrullinated peptide antibodies; RF, rheumatoid factor; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; SSA, Sjögren's syndrome antigen A; SSB, Sjögren's syndrome antigen B.

association between HTLV-1 infection and SLE has also been reported from other endemic areas.[24–26]

In agreement with the previous reports,[27,28] the present study showed no significant difference between healthy HTLV-1 carriers and individuals without the infection regarding ANA seropositivity. Of note, two ANA seropositive cases were also seroreactive for SS-B, while another study on Sjögren patients showed that anti-SS-B (La) and anti SS-A (Ro) in HAM/TSP patients and healthy carriers of the virus were similar to HTLV-1 seronegative subjects.[11] Some studies have reported an association between HTLV-1 infection and rheumatoid arthritis.[29] In the present study, the rate of RF seropositivity in HTLV-1 positive cases was almost three times higher than that in the control group, although this difference was not significant. On the other hand, this study could not find any significant difference in frequency of anti-CCP seropositivity between both study groups.

In sight of our failure to detect any relation between serum autoimmune markers with HTLV-1 infection, and because of the relatively low prevalence of autoimmune diseases, it might suggest that healthy HTLV-1 carriers do not produce autoimmune-related autoantibodies more than the population without this infection.

Taken together, the virus may be involved in cellular immunity more than humoral immunity. As far as the autoimmune disease is caused by the interaction between the environment and human genetics, as a number of commentators have shown, the overall outcome of this research was in line with other studies on this purpose. It means that in general, rheumatologic-related autoantibody formation does not arise in HTLV-1 carriers. However, there are some important questions that still should be answered.

1 Could antibody production in healthy carriers be different from HAM/TSP or ATL patients?
2 Perhaps HTLV-1 has no role in autoantibody formation but affects the course of autoimmune disorders?
3 Should other possible factors such as geographical and environmental variables be taken into consideration in autoimmune diseases related to HTLV-1?
4 What is the role of HTLV-1 associated cellular autoimmunity in these autoimmune diseases?

CONCLUSION

This study found that there are no statistically significant differences in proportions for seropositivity of autoantibodies between individuals with and without HTLV-1 infection. In other words, it could be concluded that healthy HTLV-1 carriers do not produce rheumatologic-related auto-antibodies more than other populations.

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DISCLOSURE

No conflict of interests is declared.

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ETHICS CONSIDERATIONS

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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