

## Is there any association between human T-lymphotropic virus type 1 (HTLV-1) infection and Behcet's disease?

Mohammad Javad Yazdanpanah<sup>1</sup>, Mohammad Reza Hedayati-Moghaddam<sup>2,3</sup>, Maryam Sahebari<sup>3</sup>, Mahmoud Mahmoudi<sup>4</sup>, Mehran Radfar<sup>5</sup>, Elham Vosoughi<sup>1</sup>, Habibollah Esmaily<sup>6</sup>, Zahra Mirfeizi<sup>3\*</sup>

<sup>1</sup>Cutaneous Leishmaniasis Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. <sup>2</sup>Blood Borne Infections Research Center, Academic Center for Education, Culture & Research (ACE-CR), Razavi Khorasan Branch, Mashhad, Iran. <sup>3</sup>Rheumatic Diseases Research Center (RDRC), School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. <sup>4</sup>Immunology Research Center, Bu-Ali Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran. <sup>5</sup>Health Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. <sup>6</sup>Health Sciences Research Center, Department of Biostatistics and Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran

Both human T-cell lymphotropic virus type 1 (HTLV-1) infection and Behcet's disease (BD) are common to a similar geographic area. Furthermore, some clinical presentations of BD and HTLV-1 infection, such as ocular lesions and neurologic involvement, are the same. The aim of this study was to assess a possible association between BD and HTLV-1 infection.

In this case-control study, the HTLV-1 infection frequency in BD patients was compared with that for the general population. The case group consisted of 68 patients with a definite diagnosis of BD who referred to a research center at Mashhad University of Medical Sciences in Mashhad, Iran. The control group consisted of 210 healthy individuals selected from the general population of Mashhad. The presence of HTLV antibodies in the sera was assessed using enzyme-linked immunosorbent assay and the sero-reactive samples were confirmed by polymerase chain reaction.

HTLV-1 infection was detected in 4.41% (3/68) and 1.43% (3/210) of cases and controls, respectively; however, the difference was not statistically significant ( $P$  value = 0.16).

The prevalence of HTLV1 infection in patients with BD was three-fold higher than in the general population, which suggests an association between these two conditions.

**Keywords:** Behcet's disease, HTLV-1 infection, Prevalence, Case-control study

### Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a member of the retroviridae family [1, 2]. It can be transmitted by blood transfusion, unprotected sexual contact and from mother to the child through breast feeding [3-5]. It is estimated that 5-10 million persons worldwide are infected by HTLV-1 [6]. This virus is endemic to southwestern Japan, the Caribbean, sub-Saharan Africa, South America and northeastern Iran [7-10].

HTLV-1 infection is the causative agent of adult T-cell leukemia-lymphoma, HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) and HTLV-1 associated uveitis (HAU) [1]. Studies suggest that a number of autoimmune disorders of unknown etiology, such as Sjogren syndrome, rheumatoid arthritis and sarcoidosis are probably associated with HTLV-1 infection [11-13].

Behcet's disease (BD) is a chronic autoimmune disorder characterized by recurrent oral and genital aphthosis ul-

cers, ocular and cutaneous lesions as well as cardiovascular and neurologic involvement. [14-16]. In some cases, the clinical presentations of BD and HTLV-1 infection, such as ocular lesions and neurologic involvement, are the same. Uveitis is one of the most common clinical characteristics of BD and can lead to blindness. Uveitis associated with HTLV-1 infection is an intraocular inflammation characterized by acute granulomatous or non-granulomatous inflammation associated with retinal vascular changes and vitreous opacities [17]. Furthermore, oral aphthosis lesions, a major symptom of BD, have been reported to be more common among patients with HTLV-1 infection than in the general population [18]. In addition, the patients from areas with higher rates of BD are expected to present more severe features of the disease [19].

Behçet's disease is especially common in the Mediterranean region, the Far East and countries located between the 30° and 45° latitude in Asia and Europe, which corresponds to the Old Silk Road. This road is an ancient trad-

ing route stretching from the Mediterranean, across the Middle East to the Far East [20, 21]. Iran is located on the Silk Road and has a high prevalence of BD with an incidence of 282 persons/year over the past 20 years. It has previously been reported that HTLV-1 infection is endemic to Mashhad in northeastern Iran [10], through which the Silk Road passed. The present study was undertaken to determine a possible association between BD and HTLV-1 infection in Mashhad, an area with a high prevalence of both conditions [10].

**Materials and Methods**

A total of 278 individuals were enrolled in this case-control study. The case group consisted of 68 BD patients who referred to the Rheumatic Diseases Research Center of Mashhad University of Medical Sciences in Mashhad, Iran from April 2012 to March 2013. A definite diagnosis of the disease was made based on international diagnostic criteria for BD [22, 23]. Aphthous stomatitis, genital aphthous lesions, skin manifestations, joint swelling and pain and a pathergy test were investigated in the case group. The control group comprised 210 age- and sex-matched healthy individuals selected randomly from the participants in a community-based survey conducted in 2009 by the Academic Center for Education, Culture and Research (ACE-CR), Razavi Khorasan Branch in Mashhad to evaluate the prevalence of HTLV-1 infection in its general population [10]. For each person in the case group, three persons with matched gender and age were placed in the control group.

Five milliliters of blood were obtained from each person and the serum specimens were stored at -20°C. Writ-

ten informed consent was obtained from each patient. The presence of anti-HTLV-1 antibodies was assessed using enzyme-linked immunosorbent assay (DIA.PRO Diagnostics; Italy) according to manufacturer instructions. Each sero-reactive sample was re-examined using conventional polymerase chain reaction for confirmation.

The data was analyzed using SPSS software (ver. 19). The descriptive data was summarized as mean plus standard deviation. The chi-square test and, if needed, Fisher's exact test were used to examine the frequency of HTLV-1 infection between the cases and controls. A *P* value of less than 0.05 was considered statistically significant.

**Results**

The mean age of the participants was 32.30 ± 9.23 and 32.38 ± 9.31 years in the case and control groups, respectively (*P* value = 0.956). In both groups, 50% of the individuals were male and 50% were female (*P* value = 1.000). Aphthous stomatitis, genital aphthous lesions, skin manifestations, joint swelling and pain and a positive pathergy test were observed in 79.41% (54/68), 51.47% (35/68), 35.19% (19/54), 24.53% (13/53) and 42.65% (29/68) of patients with BD, respectively.

HTLV-1 infection was found in 3 out of 68 cases (4.41%) in the case group and in 3 out of 210 controls (1.43%); however, the difference was not statistically significant (OR = 3.2; CI 95%: 0.6-16.2; *P* value = 0.16). Moreover, there was no difference in the frequency of symptoms and signs of the disease between the HTLV-1-positive and HTLV-1-negative patients with BD (Table 1).

**Table 1.** Clinical features of Behcet's disease in patients with and without HTLV-1 infection

Clinical manifestation	HTLV-1 infection		P value
	Yes	No	
Positive pathergy test	33.33% (1/3)	43.08% (28/65)	0.6
Aphthous stomatitis	100% (3/3)	78.46% (51/65)	0.5
Genital aphthous lesions	0% (0/3)	53.85% (35/65)	0.1
Joint swelling and pain	0% (0/2)	25.49% (13/51)	0.5
Skin manifestations	0% (0/2)	36.54% (19/52)	0.4

**Discussion**

A three-fold higher prevalence of HTLV-1 infection among BD patients compared to general population was observed; however, this difference was not statistically significant (*P* value = 0.16). BD is a chronic autoimmune disorder affecting tissues and organs of the body [20, 24]. The main etiology of the disease is unknown. Epidemi-

ological findings indicate that an autoimmune process is caused by an environmental factor in a genetically predisposed individual. A bacterial or viral infectious agent may act through molecular mimicry and, subsequently, the disease may be prolonged by an abnormal immune response to an autoantigen in the absence of ongoing infection. For instance, because of clinical evidence that unhygienic conditions are more frequently noted in the oral cavity of BD

patients, a relationship between streptococcal infection and BD has been proposed [25]. The relation between the development of BD and streptococcal infection is not distinct; however, the uncommon *Streptococcus sanguinis* serotypes (KTH-1) and antibodies against the bacteria were shown to have increased significantly in the oral flora and serum of BD patients in comparison with healthy controls [26]. Choi et al. [27] found that anti-*S. cerevisiae* antibodies (ASCAs) predominate in intestinal BD and show an increase in the healthy relatives of patients. They reported that the ASCA-positive rate was 44.3% in the BD, but this did not depend on the clinical findings at the time of diagnosis or to the rate of the disease relapse.

The relation between BD and viral infections is not well known. Behçet proposed a viral etiology initially [28]. Evidence of ongoing infection with various viral agents has been investigated; however, only a history of previous infection and/or seropositivity has been regularly found [28, 29]. Although herpetiform ulcers are unusual, herpes simplex virus type 1 (HSV-1) is currently the most common virus associated with BD. In a higher percentage of patients with BD than controls were shown to have HSV DNA and serum antibodies against the virus [30-32]. Additionally, circulating immune complexes with the HSV-1 antigen have been reported [33].

HSV DNA has been confirmed in genital and intestinal ulcers aside from oral ulcers. Anti-HSV immunity is also common in normal subjects and findings related to the therapeutic effects of antiviral treatment in BD are rare and controversial [34, 35]. Sohn et al. reported Behçet's disease-like symptoms, including skin ulcers and vascular inflammation, following inoculation with HSV of mice [36, 37]. Viral agents such as hepatitis C, parvovirus B19, cytomegalovirus, Epstein-Barr and the varicella-zoster may also be indicated in the development of BD [35]. Baskan et al. reported that the presence of parvovirus B19 DNA in the non-ulcerative lesions of BD patients was significantly higher than on the skin of the healthy individuals [38].

Both HTLV-1 infection and BD are more common in the same geographical area and share common clinical features [7, 10, 15, 18]. A diagnosis of HAM and HAU was confirmed in a Japanese woman with a clinical diagnosis of neuro-Behçet's disease referred because of spastic paraparesis and recurrent uveitis [39]. The authors detected high titers of anti-HTLV-1 antibodies in her serum, cerebrospinal fluid and aqueous humor. They concluded that HAM, together with uveitis, resembles neuro-Behçet's disease; however, they believed that these two conditions should be differentiated [39]. Furthermore, in a comparative study performed in Mashhad, Iran, recurrent aphthous stomatitis was found to be the most prevalent manifestations in HTLV-1 seropositive patients [40]. The current findings indicate a considerably higher frequency of HTLV-1 infection among the BD patients compared to the general population, but the difference was not statistically significant and no significant association was observed between the clinical characteristics of BD and HTLV-1 infection. In addition, in a survey conducted by Yosipovitch et al. [41], no positive case of HTLV-1 was detected among 18 patients with BD.

#### Limitations of study

Future studies with larger sample sizes are required to clarify any association between HTLV-1 and Behçet's disease.

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#### Conflict of interest

The authors declare no conflicts of interest related to this study.

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