

## Autoimmune Thyroiditis in Patients with Myelopathy/Tropical Spastic Paraparesis and in HTLV-1 Carriers in Mashhad, Northeastern Iran

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Received: October 17, 2008

Accepted: October 24, 2008

**Abstract.** There are some reports about the association of autoimmune thyroid diseases with human T-cell leukemia virus type-I (HTLV-I) infection. The objective of this study was to estimate the seroprevalence rates of antithyroid antibodies in HTLV-I carriers and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients in Mashhad, northeastern Iran, in order to determine any association between HTLV-I infection and Hashimoto's thyroiditis (HT).

**Methods:** Forty-six HTLV-I infected patients (24 patients with HAM/TSP and 22 asymptomatic carriers) and 40 HTLV-I seronegative healthy individuals were screened for the presence of thyroid autoantibodies. The diagnosis of Hashimoto's thyroiditis was based on the presence of positive thyroid autoantibodies (anti-thyroid peroxidase and/or antithyroglobulin) and at least one of two additional criteria (hypothyroidism and/or goiter). Analysis of the data was done using the Fisher-Exact test and SPSS statistical software version 13.0. Any P value below 0.05 was considered statistically significant.

**Results:** We found thyroid autoantibodies in 14 (63.6%) of 22 asymptomatic carriers, 6 (25%) of 24 patients with HAM/TSP, and 3 (7.5%) of 40 HTLV-I seronegative healthy individuals. We found Hashimoto's thyroiditis in 45.4% of asymptomatic carriers, 25% of HAM/TSP patients, and 5% of seronegative healthy individuals. The percentage of patients with Hashimoto's thyroiditis was significantly higher ( $P < 0.01$ ) than the percentage in healthy seronegative individuals.

**Conclusion:** This study demonstrates a high prevalence of Hashimoto's thyroiditis in the HAM/TSP patients and the HTLV-I carriers in Mashhad. Our findings suggest an association between HTLV-I infection and Hashimoto's thyroiditis in our region.

**Keywords.** Hashimoto's thyroiditis • HTLV-1 • Mashhad, Iran • Myelopathy/tropical spastic paraparesis • Thyroglobulin antibodies • Thyroid peroxidase antibodies

### Introduction

Human T-cell leukemia virus type-I (HTLV-I) is a human retrovirus endemic in southern Japan, intertropical Africa, Melanesia, Latin America, and the Caribbean basin.<sup>[1]</sup> HTLV-I is etiologically associated with adult T-cell leukemia<sup>[2]</sup> and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).<sup>[3][4]</sup> HTLV-I may also cause some other inflammatory disorders such as uveitis,<sup>[5]</sup> chronic arthropathy,<sup>[6]</sup> pulmonary alveolitis,<sup>[7]</sup> and Sjögren's

syndrome.<sup>[8]</sup> The possible role of HTLV-I in thyroid diseases was initially raised by reports of Hashimoto's thyroiditis in HTLV-I carriers and patients with HAM/TSP.<sup>[9][10]</sup> Graves' disease has also been observed in HTLV-I carriers.<sup>[11][12]</sup> HTLV-I seropositivity has been a risk factor for thyroid disorders in epidemiological studies in Japan.<sup>[10][13][14][15]</sup>

The possible pathogenic role of HTLV-I in thyroid diseases is supported by many findings: HTLV-I envelope protein and tax mRNA have been detected in follicular epithelial cells of the thyroid

tissues of a patient with Hashimoto's thyroiditis;<sup>[16]</sup> tax mRNA was also found in infiltrating lymphocytes in the interfollicular space;<sup>[16]</sup> and HTLV-I proviral DNA and HTLV-I have been detected in the thyroid tissue of patients with Hashimoto's thyroiditis and Graves' disease.<sup>[16][17]</sup>

The virus is also endemic in Mashhad in north-eastern Iran.<sup>[18]</sup> To our best knowledge, there has been no study in our region of the prevalence of Hashimoto's thyroiditis among HTLV-I carriers or among HAM/TSP patients. This study had two objectives: to estimate the seroprevalence rates of anti-thyroid antibodies in HTLV-I carriers and HAM/TSP patients in Mashhad, and to determine whether we would find an association in the patients between Hashimoto's thyroiditis and HTLV-I.

### Methods and Patients

Blood samples were collected from 46 HTLV-I infected patients, 22 asymptomatic carriers (13 females and 9 males, 22-70 years old, mean age: 42.58±14.49), and 24 patients with HAM/TSP (17 females and 7 males, 17-64 years old, mean age: 38.04±11.04). Forty HTLV-I seronegative healthy individuals (26 female and 14 males, 17-65 years old, mean age: 36.84±16.32) served as normal controls. The control subjects did not have a history of thyroid or autoimmune diseases.

The diagnosis of Hashimoto's thyroiditis was based on the presence of positive thyroid autoantibodies, thyroid peroxidase (TPO) and/or thyroglobulin (Tg), and at least one of two additional criteria: hypothyroidism and/or goiter. Antibodies to TPO and Tg were determined by RIA (Aeskalisa a-TPO, Orgentec Diagnostica, Germany). Diagnosis of HAM/TSP was based on the World Health Organization diagnosis guidelines.<sup>[19]</sup> All patients (HTLV-I asymptomatic carriers and those with HAM/TSP) and all HTLV-I-seronegative healthy controls were Iranians living in Mashhad (HTLV-I endemic city), the northeast area of Iran.

### Statistical Analyses

Data were descriptively expressed as mean±SD or number and percent. Statistical analysis was done by using the Fisher-Exact test with statistical software SPSS version 13.0. Any P value below 0.05 was considered statistically significant. The Endocrine Research Committee of Mashhad University

reviewed all aspects of the research and approved the protocol.

### Results

Thyroid autoantibodies were positive in 14 (63.6%) of 22 asymptomatic carriers, 6 (25%) of 24 patients with HAM/TSP, and 3 (7.5%) of 40 HTLV-I seronegative healthy individuals. In the HTLV-I carrier groups, 4 patients had subclinical hypothyroidism and 6 patients had euthyroid firm goiter. In the HAM/TSP group, 4 patients had subclinical hypothyroidism and 2 patients had euthyroid firm goiter. Seronegative healthy individuals were euthyroid and 2 of them had firm goiter. Hashimoto's thyroiditis was found in 45.4% of asymptomatic carriers, 25% of HAM/TSP patients, and 5% of seronegative healthy individuals. Therefore, the percentage of patients with Hashimoto's thyroiditis was significantly higher ( $P<0.01$ ) than the percentage in healthy seronegative individuals.

### Discussion

HTLV-I is a human retrovirus endemic in some areas of the world.<sup>[1]</sup> HAM/TSP is the major syndrome caused by HTLV-I, but the virus may also cause a systemic immune-mediated inflammatory disease involving many tissues including the thyroid gland. Correlation of autoimmune thyroid diseases and HTLV-I infection were investigated recently, and the role of HTLV-I in the pathogenesis of autoimmune thyroid diseases has been demonstrated in animals and humans.<sup>[20][21][22][23][24]</sup>

Genetic factors including human leukocyte antigen and cytotoxic T lymphocyte antigen-4 (CTLA-4) are involved in autoimmune thyroid diseases.<sup>[25][26]</sup> However, HTLV-I infection is not associated with CTLA-4 polymorphisms in either Hashimoto's thyroiditis patients or controls.<sup>[27]</sup> HTLV-I infection, then, does not appear to be regulated by genetic factors, and it may cause Hashimoto's thyroiditis as an independent, purely environmental factor.

The HTLV-I proviral load is thought to be a major determinant of HTLV-I-associated diseases. The proviral load is higher in the peripheral blood of patients with HAM/TSP than in the blood of asymptomatic carriers.<sup>[28]</sup> It is also higher in the peripheral blood of HTLV-I-infected patients with either Hashimoto's thyroiditis or Graves' disease than in

HTLV-I asymptomatic carriers.<sup>[29]</sup> Similarly, patients with HTLV-I-associated uveitis and HTLV-I-seropositive patients with arthritis or connective tissue disease have a higher proviral load than asymptomatic carriers.<sup>[30][31]</sup>

Involvement of HTLV-I in the pathogenesis of autoimmune thyroid disease in Japan, where this retrovirus is endemic, has been extensively investigated. Kawai et al. reported that the prevalence of HTLV-I antibodies in Hashimoto's thyroiditis patients, residents of the Tokushima and Kochi prefectures in Japan, was 6.3%, which was significantly higher than the expected frequency of 2.2%.<sup>[10]</sup>

Mizokami et al. also reported that the prevalence of HTLV-I antibodies was significantly higher in patients with either antithyroid antibody-positive chronic thyroiditis (7.4%) or Graves' disease (7%) than the expected frequency in Fukuoka prefecture, Japan.<sup>[13]</sup> Mine et al. found that the frequency of antithyroid antibodies in blood donors with HTLV-I antibodies was significantly higher (7.9%) than that in control donors without the HTLV-I antibodies.<sup>[14]</sup> Akamine et al. also found a high prevalence of positivity for thyroid autoantibodies in adult T-cell leukemia patients (40.4%) and HTLV-I carriers (30%).<sup>[15]</sup>

Mashhad, a city in northeastern Iran, is also an endemic area for HTLV-I.<sup>[18]</sup> The present study determined the seroprevalence rates of antithyroid antibodies in HTLV-I carriers and HAM/TSP patients for the first time in Iran. The study also provides data supporting the role of HTLV-I in the development of thyroid diseases in our region.

Hashimoto's thyroiditis was found in 45.4% of asymptomatic carriers of HTLV-I and 25% of HAM/TSP patients. These percentages were significantly higher ( $P < 0.01$ ) than the percentage of Hashimoto's thyroiditis in healthy seronegative individuals (5%).

## Conclusion

This study demonstrates a high prevalence of positivity for antithyroid autoantibodies and Hashimoto's thyroiditis in HAM/TSP patients and HTLV-I carriers in Mashhad. There is, then, an association between HTLV-I infection and Hashimoto's thyroiditis in our region.

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