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Association of active human herpesvirus-6 (HHV-6) infection with autoimmune thyroid gland diseases.

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OBJECTIVES: Viral infections frequently have been cited as important environmental factors implicated in the onset of autoimmune thyroiditis (AIT). The aim of this study was to determine the involvement of HHV-6 infection in the development of autoimmune thyroiditis.

METHODS: This study included 45 patients (42 female and 3 male; median age 47.00 IQR 38.50-57.00) with histologically, laboratory, and clinically confirmed autoimmune thyroiditis, as well as 30 autopsied subjects (26 female and 4 male; median age 58.50, IQR 51.50-67.00) without thyroid pathologies and 30 healthy blood donors (25 female and 5 male; median age 33.50, IQR 27.75-44.25) as controls. Results were obtained by applying molecular virology and immunohistochemistry techniques.

RESULTS: The presence of persistent HHV-6 infection in AIT patients was significantly higher (p 0.0058) than in the control group (44/45 (98%) vs. 23/30 (77%), respectively). Also, a significantly higher frequency of HHV-6 activation marker (U79/80 mRNA) was found in patients' thyroid gland tissue samples with AIT in comparison with the control group (18/44 (41%) vs. 1/17 (6%), respectively; p 0.0118). The median HHV-6 load was found to be higher in patients with active viral infection than in patients without it (2147, IQR 971-4188 vs. 551, IQR 145-1589 copies/ 1×10(6) cells; p 0.003). The presence of HHV-6 antigen expression was demonstrated in intrafollicular cellular clusters and immunohistochemistry indicated thyrocytes in the follicle wall.

CONCLUSIONS: **These findings provide evidence of strong HHV-6 infection association with AIT development.**

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1. J Med Virol. 2013 Nov;85(11):1925-34. doi: 10.1002/jmv.23670.

Selective reactivation of human herpesvirus 6 in patients with autoimmune connective tissue diseases.

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Viral infections have been associated with autoimmune connective tissue diseases. To evaluate whether active infection by Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus (HHV)-6, -7, -8, as well as parvovirus B19 (B19V) occur in patients with autoimmune connective tissue diseases, viral DNA loads were assessed in paired samples of serum and peripheral blood mononuclear cells (PBMCs) of 115 patients affected by different disorders, including systemic sclerosis, systemic, and discoid lupus erythematosus, rheumatoid arthritis, and dermatomyositis. Two additional groups, patients affected by inflammatory diseases (n=51) and healthy subjects (n=58) were studied as controls. The titers of anti-HHV-6 and anti-EBV antibodies were also evaluated.
Cell-free HHV-6 serum viremia was detected in a significantly higher proportion of connective tissue diseases patients compared to controls (P<0.0002); a significant association between HHV-6 reactivation and the active disease state was found only for lupus erythematosus (P=0.021).
By contrast, the rate of cell-free EBV viremia was similar in patients and controls groups.
Cell-free CMV, HHV-8, and B19V viremia was not detected in any subject.
Anti-HHV-6 and anti-EBV early antigen IgG titers were both significantly higher in autoimmune diseases patients as compared to healthy controls, although they were not associated with the presence of viremia.
EBV, HHV-6, -7 prevalence and viral load in PBMCs of patients with connective tissue diseases and controls were similar.
These data suggest that HHV-6 may act as a pathogenic factor predisposing patients to the development of autoimmune connective tissue diseases or, conversely, that these disorders may predispose patients to HHV-6 reactivation.

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Active human herpesvirus 6 infection in patients with multiple sclerosis.

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CONTEXT: Human herpesvirus 6 (HHV-6) has been linked with multiple sclerosis (MS).
OBJECTIVES: To determine HHV-6 viral load in patients with MS, and to analyze separately its 2 variants, HHV-6A and HHV-6B.
PATIENTS AND METHODS: We analyzed 149 blood and serum samples; 103 were from patients with relapsing-remitting MS (33 during an MS relapse and 70 during remission), and 46 were from healthy blood donors. To determine whether the HHV-6 genome and its variants were present, we analyzed viral DNA using quantitative real-time polymerase chain reaction, which has a sensitivity of 1 copy.
RESULTS: We found HHV-6 DNA in the peripheral blood mononuclear cells of 53.4% of patients and 30.4% of healthy blood donors; HHV-6A was found in 20.4% of patients and 4.4% of controls, and HHV-6B was found in 33.0% vs 26.1%, respectively. Mean viral load in both groups was 7.4 copies of HHV-6 per microgram of DNA (range, 1-15 copies). Analysis of serum samples showed that none of the healthy blood donors were positive for HHV-6, although 14.6% of patients were positive for the virus, specifically the HHV-6A variant. There was no difference between patients during remission or relapse. Mean viral load was 26.3 copies/microg microgram of DNA (range, 1-86 copies).
CONCLUSIONS: Despite the low viral load and the lack of clinical correlation, and given the biological characteristics of the virus, **our results suggest that there was active HHV-6A infection in 14.6% of patients with MS**. Further quantitative real-time polymerase chain reaction studies will help us understand the clinical significance of such a low viral load.

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1. PLoS Pathog. 2012;8(10):e1002951. doi: 10.1371/journal.ppat.1002951. Epub 2012 Oct 4.

Virologic and immunologic evidence supporting an association between HHV-6 and Hashimoto's thyroiditis.

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Hashimoto's thyroiditis (HT) is the most common of all thyroid diseases and is characterized by abundant lymphocyte infiltrate and thyroid impairment, caused by various cell- and antibody-mediated immune processes. Viral infections have been suggested as possible environmental triggers, but conclusive data are not available. We analyzed the presence and transcriptional state of human herpesvirus 6 (HHV-6) in thyroid fine needle aspirates (FNA) and peripheral blood mononuclear cells (PBMCs) from 34 HT patients and 28 controls, showing that **HHV-6 DNA prevalence (82% vs. 10%, p≤0.001) and viral load were significantly increased in FNA from HT patients, and thyrocytes from HT FNA displayed a 100-fold higher HHV-6 DNA load compared to infiltrating lymphocytes**. In addition, while HHV-6 was strictly latent in positive samples from controls, a low grade acute infection was detected in HT samples. HHV-6 variant characterization was carried out in 10 HT FNA samples, determining that all specimens harbored HHV-6 Variant A.The tropism of HHV-6 for thyroid cells was verified by infection of Nthy-ori3-1, a thyroid follicular epithelial cell line, showing that thyrocytes are permissive to HHV-6 replication, which induces de novo expression of HLA class II antigens. Furthermore, HHV-6-infected Nthy-ori3-1 cells become targets for NK-mediated killing, NK cells from HT patients show a significantly more efficient killing of HHV-6 infected thyroid cells than healthy controls, and HT patients have increased T-cell responses to HHV-6 U94 protein, associated to viral latency. **These observations suggest a potential role for HHV-6 (possibly variant A) in the development or triggering of Hashimoto Thyroiditis**.

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