Association of human T lymphotropic virus type I with Sjögren syndrome

Sjögren syndrome (SS) is an autoimmune disease caused by a combination of genetic and environmental factors. The most important environmental factor is viral infection. The retrovirus human T lymphotropic virus type I (HTLV-I) is deemed as an SS pathogen, because anti-HTLV-I antibodies were positive in 23% of patients with SS but only in 3.4% of control subjects (blood donors).[1] The patients with SS in that study, however, were limited to those who visited the hospital, and the control is not screened for SS, a bias may have been present. Thus, in the present study, we measured anti-HTLV-I antibodies in 852 Nagasaki atomic bomb survivors who had previously been screened for SS.

Between November 2002 and October 2004, 1008 Nagasaki atomic bomb survivors who had been followed biennially since 1958 at the Radiation Effects Research Foundation (RERF),[2] answered a questionnaire concerning ocular and oral symptoms and were screened for anti-SS-A/Ro, anti-SS-B/La antibodies and rheumatoid factor. We then examined them for SS using American–European Consensus Group criteria[3] and its modifications, including the tear flow test (Schirmer-I test), salivary flow test (Saxon test), cornea and conjunctiva staining test, salivary ultrasonography and salivary MRI.[4] We found 23 SS cases, a prevalence of 2.3%.[4] From April 2006 to June 2008, 852 participants (18 with SS, 335 men and 517 women, average age 71.1 years) underwent HTLV-I antibody measurements. RERF's Human Investigation Committee reviewed and approved the study protocol, and all participants provided written informed consent.

Of the 852 participants, 75 (8.8%) were anti-HTLV-I antibody positive by chemiluminescent enzyme immunoassay (Fujirebio, Tokyo, Japan) and western blotting (BML, Tokyo, Japan). A total of 5 (6.7%) of the seropositive subjects and 13 (1.7%) of the seronegative subjects were diagnosed as having SS. In all, 5 (27.8%) of the 18 SS participants and 70 (8.4%) of the 834 non-SS participants had anti-HTLV-I antibodies (p=0.016, Fisher exact test). Prevalence of women (57/75, 76%, 460/777, 59%, p=0.005) and positive anti-SS-A/Ro antibodies (7/75, 9.3%, 23/777, 3.4%, p=0.020) and titre of rheumatoid factor (9.8 U/ml, 7.7 U/ml, p=0.038) were also significantly higher among HTLV-I seropositive group than seronegative group. The finding that HTLV-I infection was predominant in women may partly explain the predominance of SS in women. The prevalence of SS-B/La antibodies was similar for the two groups (1/75, 1.3%, 7/777, 0.9%). An age-adjusted and sex-adjusted OR of having SS for those in the HTLV-I seropositive group was 3.68 (95% CI, 1.26 to 10.75, p=0.014) by a linear logistic model. That suggests a possible association between HTLV-I infection and SS as reported in previous immunological studies.[5–7]

Table 1 Characteristics of Sjögren syndrome (SS) according to anti-human T lymphotropic virus type I (HTLV-I) antibody status

	HTLV-I positive SS (n=5)	HTLV-I negative SS (n=13)
Mean±SD age, years	71.4±5.8	71.7±5.6
Sex (male:female)	0:5	3:10
Sicca symptoms, N (%)	4 (80)	9 (69)
Dry eye signs, N (%)	5 (100)	9/9* (100)
Dry mouth signs, N (%)	4 (80)	10 (77)
Anti-SS-A Ab, N (%)	4 (80)	10 (77)
Anti-SS-B Ab, N (%)	1 (20)	3 (23)
Anticentromere Ab, N (%)	0 (0)	2/12* (17)
Extraglandular manifestations, N (%)	3 (60)	2 (15)
Secondary SS, N (%)	1 (20)	2 (15)
RF positive, N (%)	0 (0)	4 (31)

*Number was reduced because not all the participants agreed to take full examinations.
Ab, antibodies; RF, rheumatoid factor.

The prevalence of sicca symptoms, signs and positive autoantibodies was similar between the HTLV-I positive and negative SS groups (table 1). The frequency of extraglandular manifestations tended to be higher in HTLV-I seropositive group than in HTLV-I seronegative group (table 1), which supports the previous report.[8]

Our results suggest that the association between HTLV-I and SS is mediated through anti-SS-A/Ro antibodies, because the association between being anti-HTLV-I antibody positive and SS disappeared when anti-SS-A/Ro antibodies were incorporated in the analysis (data not shown). While genetic and environmental factors interact in the development of SS, HTLV-I may be an immune-activating pathogen for SS through anti-SS-A/Ro antibody production. Further studies are needed to confirm this.

All participants in the present study were atomic bomb survivors, but no association has been reported between radiation dose and either SS[4] or HTLV-I infection,[9] nor did we find a significant association between radiation dose by DS02[10] and HTLV-I in the present study. Thus, our data should be generalisable to the Japanese population.

In this first epidemiological study of measuring anti-HTLV-I antibodies in SS and non-SS participants, we confirmed the

association between HTLV-I infection and SS or anti-SS-A/Ro antibodies.

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