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Original Article

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Human T-Cell Leukemia Virus Type 1 Infection Is a Risk Factor for Atherosclerosis

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Abstract

Background: Infection, such as by human immunodeficiency virus (HIV), has been reported to cause atherosclerosis by inducing inflammation. Because human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus, as is HIV, we investigated the possible influence of HTLV-1 on the pathogenesis of atherosclerosis by use of established atherosclerosis parameters.

Methods: The study was done on Iki Island, Fukuoka, an area endemic for HTLV-1. The data of 1,424 residents who reported to an annual health check were available for analysis. Anti-HTLV-1 antibody status and factors associated with atherosclerosis were examined, including maximum intima-media thickness (Max-IMT) and brachial-ankle pulse wave velocity (PWV).

Results: HTLV-1 positive participants had significantly higher Max-IMT (1.15 ± 0.55 vs. 1.08 ± 0.61 mm, P = 0.04) and PWV (1,760.6 ± 414.5 vs. 1,657.1 ± 425.5 cm/s, P < 0.01) values than did those negative. Moreover, in multiple regression analysis (odds ratio: 1.39, P < 0.01) of participants with Max-IMT 1.1 mm or over, HTLV-1 was extracted as an independent factor for the development of atherosclerosis.

Conclusion: Our results indicate that HTLV-1 infection confers a high risk of atherosclerosis, although its opposite relation is also possible. It is important to carefully follow the health status of HTLV-1 carriers.

Keywords: HTLV-1; Atherosclerosis; IMT

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Introduction

Chronic inflammation and immune activation are major risk factors for atherosclerosis [1]. Infection with viral or bacterial agents is recognized as a possible risk factor for atherosclerosis, alongside other risk factors such as hypertension, smoking, hypercholesterolemia, hyperglycemia and genetic factors [2, 3]. Examples of viral pathogens found in atherosclerotic plaque are: hepatitis C virus (HCV), cytomegalovirus (CMV), herpes simplex viruses (HSV), human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV) [3, 4]. HIV-infected patients are at increased risk for cardiovascular disease (CVD) events, even those on antiretroviral therapy (ART) and whose HIV infection is well controlled [5, 6]. Clinical observations and imaging studies have shown an increasing prevalence of subclinical atherosclerosis in HIV-infected patients [7, 8].

Recent studies have shown that HIV infection is a predictor of increased intima-media thickness (IMT) [9, 10]. IMT is measured by high-resolution B-mode ultrasound and is used for the assessment of atherosclerosis. Increased IMT is an important predictor of future cerebrovascular and cardiovascular events [11]. A recent study reported an association between atherosclerosis and human T-cell leukemia virus type 1 (HTLV-1) in a population of elderly people in whom IMT was measured [12, 13].

HTLV-1, first diagnosed in 1980 in a patient with cutaneous lymphoma, can cause inflammatory diseases [14]. A characteristic of this virus is that over 90% of carriers remain asymptomatic. In symptomatic patients, it can cause serious disorders such as adult T-cell leukemia/lymphoma (ATLL), HTLV-1-associated myelopathy/tropical seizures (HAM/TSP), HTLV-1 infection-related dermatitis (IDH), Sjogren's syndrome, thyroiditis, lymphocytic pneumonia, uveitis, Behcet's disease, polymyositis and arthropathy [15]. This virus is regionally specific and is endemic to southwestern Japan, Central and South America, the Caribbean Islands, Central Australia and sub-Saharan Africa [16].

Inflammation is of paramount importance in the development of atherosclerosis [17, 18], and HTLV-1 is a chronic inflammatory disease that contributes inflammatory stimulation that could initiate or exacerbate atherosclerosis. The causative factors of atherosclerosis have been reported to include an inflammatory mechanism involving the release of cytokines and chemokines. Increased levels of cytokines and local inflammatory chemokines induce leukocyte activation. As a result,

mononuclear cells infiltrate the atherosclerotic plaque [19].

To clarify the association between atherosclerosis and HTLV-1, we investigated the IMT and brachial-ankle pulse wave velocity (PWV) of residents who took a routine health examination for all ages.

Materials and Methods

Design

The area of this retrospective, cross-sectional study is Iki, an island in southwestern Japan, with a population of about 32,000. Life is similar to that of people living in other parts of Japan, fishing and agriculture are the main sources of income and HTLV-1 is endemic [20]. A free medical examination consisting of a physical examination, questionnaire, blood cell count and blood chemistry analysis including HTLV-1 antibodies was conducted. This study was approved by the Institutional Review Board of Kyushu University Hospital and was conducted in accordance with the human experimentation guidelines of the US. The study included 1,424 residents (482 male and 942 female, age range 19 - 90 years, average age 63.2 years). All participants underwent a health checkup sponsored by the local public health center in June of 2005. Participants must be 18 years of age or older to consent to participate in the health checkup, excluding those under 18 years of age and those who cannot consent to participate in the health checkup.

Height and weight were measured and body mass index (BMI) was calculated (BMI = weight/height^2 (kg/m^2)). Systolic and diastolic blood pressures (SBP and DBP) were measured at rest in a sitting position. Blood samples were collected from all of the subjects after overnight fasting, and sera were stored at -20 °C until testing for routine serum biochemistry and anti-HTLV-1 antibody tests. Serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), HbA1c and C-reactive protein (CRP) were determined by a commercial blood chemistry analysis machine in a professional laboratory. The smoking status was categorized as “none”, “past” or “present”.

Detection of anti-HTLV-1 antibody

Screening for anti-HTLV-1 antibody was done by the passive particle agglutination (PA) method (Fujirebio, Tokyo, Japan) for all samples. Positive results were confirmed by Western blot analysis according to the manufacturer’s protocol (Fujirebio, Tokyo, Japan), with bands gp46, p53, p24 and p19 indicating positivity. Samples for which the results of both methods were positive were considered positive for anti-HTLV-1 antibody and those determined to be seroreactive for anti-HTLV-1 by PA alone were considered to be negative for HTLV-1. In this study, subjects positive for anti-HTLV-1 antibody were defined as HTLV-1 carriers.

Monitoring of atherosclerosis parameters

We examined IMT, plaque and stenosis of the extra-cranial carotid arteries with B-mode ultrasound using a 7.5 MHz linear array transducer and a high-resolution instrument (Fukuda Denshi, Japan). Carotid artery echoes were measured by trained physicians using standardized procedures. IMT is defined as the distance between two echo lines separated by a hypoechoic or anechoic space. The outer line corresponds to the medial-adventitial border and the inner line represents the luminal-intimal border. The IMT is measured at the end of the diastole phase at locations 20, 25 and 30 mm proximal to the flow divider in the distal wall of the right and left common carotid arteries. The maximum IMT value was defined as Max-IMT. The Max-IMT of the common carotid artery was measured in the right and left carotid arteries, and the larger value was used. The upper limit of normal for IMT was set at 1.0 mm [21, 22], and 1.1 mm or more was considered atherosclerotic plaque. According to the criteria of the carotid ultrasound examination guidelines, we classified Max-IMT 1.1 mm or over as atherosclerosis [23].

PWV was measured using a VP-1000 (BP-203RPEII; Colin Corp., Ltd, Osaka, Japan). Pneumatic cuffs were placed on each arm and ankle, electrocardiographic electrodes were placed on each wrist and a microphone for heart sound detection was placed on the left end of the sternum to record the volume waveform of the brachial and ankle arteries. PWV was automatically calculated from the transit time of the pulse wave by the length of the arterial segment between the brachial artery and ankle (which was automatically calculated from the body height). Framingham score was used as an independent variable for risk stratification, and PWV 1,400 (cm/s) or over was defined as atherosclerotic CVD [24].

Statistical analysis

Values are described as mean ± standard deviation (SD). Items for analysis included age, sex, BMI, blood pressure, FBG, HbA1c, smoking history, TC, LDL-C, TG, HDL-C, CRP, Max-IMT and PWV. The unpaired *t*-test and Mann-Whitney U analysis were used for analysis of differences in means between the HTLV-1 carriers and antibody-negative control participants. Multivariable-adjusted analysis was used to determine correlations between Max-IMT 1.1 mm or over and other associated variables. For all tests, a “P” value less than 0.05 was considered to have statistical significance.

All statistical analyses were performed using EZR [25], a modified version of R commander.

Results

Clinical characteristics

Table 1 shows the age- and sex-based prevalence of anti-HTLV-1 antibody among the residents of Iki Island. Of the 1,424 residents who participated in this study, 272 (19.1%)

Table 1. Age- and Sex-Specific Prevalence of Anti-HTLV-1

Age (years)	Male		Female		Total	
	No. tested	Anti-HTLV-1 positive, No. (%)	No. tested	Anti-HTLV-1 positive, No. (%)	No. tested	Anti-HTLV-1 positive, No. (%)
10 - 19	0	0	1	0	1	0
20 - 29	2	0	8	1 (12.5)	10	1 (10.0)
30 - 39	31	1 (3.2)	57	4 (7.5)	88	5 (5.7)
40 - 49	48	3 (6.3)	90	7 (7.8)	138	10 (7.2)
50 - 59	63	7 (11.1)	207	30 (14.5)	270	37 (13.7)
60 - 69	143	20 (14.0)	301	77 (25.6)	444	97 (21.8)
70 - 79	161	34 (21.1)	249	75 (30.1)	410	109 (26.6)
80 or over	34	4 (11.8)	29	9 (31.0)	63	13 (20.6)
Total	482	69 (14.3)	942	203 (21.5)	1424	272 (19.1)

HTLV-1: human T-cell leukemia virus type 1.

were HTLV-1 positive, with the prevalence significantly higher for residents 60 years and older than for those under 60 years ($P < 0.01$). All 272 HTLV-1 positive are asymptomatic carriers. The remaining 1,152 were HTLV-1 negative. The clinical characteristics of the HTLV-1 positive and HTLV-1 negative groups are shown in Table 2. Age, HbA1c and smoking were significantly different between the two groups.

Comparison of the atherosclerosis parameters

The Max-IMT and PWV levels of the HTLV-1 positive and negative groups are shown in Table 2. The Max-IMT (1.15 ± 0.55 vs. 1.08 ± 0.61 mm, $P = 0.04$) and PWV (1,760.6 ± 414.5 vs. 1,657.1 ± 425.5 cm/s, $P < 0.01$) of the HTLV-1 positive group was significantly higher than that of the HTLV-1 negative group.

Risk factors for atherosclerosis by multiple regression analysis

Table 3 shows that the multivariable-adjusted odds ratio (OR) (95% confidence interval (CI)) per 1.1 mm over increase in Max-IMT was 1.39 (1.02 - 1.89) ($P < 0.01$). We adjusted for age, sex, smoking, SBP, BMI, PWV and HbA1c. Importantly,

Table 2. Clinical Characteristics

	HTLV-1 positive (n = 272)	HTLV-1 negative (n = 1,152)	P-value
Age (years)[a]	66.7 ± 9.7	61.1 ± 13.1	< 0.01
Male (%)	69 (25.4)	413 (35.8)	0.179
BMI (kg/m^2)[a]	22.8 ± 2.9	23.2 ± 3.3	0.100
SBP (mm Hg)[a]	135.9 ± 19.5	135.5 ± 21.2	0.723
DBP (mm Hg)[a]	78.8 ± 9.7	79.5 ± 11.0	0.307
FBG ≥ 126 (mg/dL) (%)	16 (5.9)	47 (4.1)	0.255
HbA1c ≥ 6.5% (%)	16 (5.9)	28 (2.1)	< 0.01
Smoking (past (present)) (%)	46 (16.9)	267 (23.2)	0.03
Total cholesterol[a]	207.4 ± 31.9	207.8 ± 34.5	0.143
Triglyceride[a]	100.9 ± 48.8	101.0 ± 60.2	0.495
HDL-C[a]	62.8 ± 15.6	63.5 ± 15.6	0.249
LDL-C[a]	124.4 ± 28.9	124.1 ± 31.4	0.444
C-reactive protein[a]	0.068 ± 0.004	0.066 ± 0.002	0.720
Max-IMT (mm)	1.15 ± 0.55	1.08 ± 0.61	0.04
PWV (cm/s)	1,760.6 ± 414.5	1,657.1 ± 425.5	< 0.01

[a]Average ± standard deviation (range). HTLV: human T-cell leukemia virus type 1; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Max-IMT: maximum intima-media thickness; PWV: brachial-ankle pulse wave velocity.

Table 3. Impact of HTLV-1 on Carotid Plaque

	Max-IMT 1.1 mm or over	Crude OR	95% CI	P-value	Multivariable-adjusted OR	95% CI	P-value
HTLV-1 positive (%)	103 (37.9)	1.66	1.25 - 2.18	< 0.01	1.39	1.02 - 1.89	< 0.01
HTLV-1 negative (%)	310 (26.9)	Reference			Reference		

HTLV-1: human T-cell leukemia virus type 1; Max-IMT: maximum intima-media thickness; OR: odds ratio; CI: confidence interval.

in addition to these common, well-known atherosclerotic risk factors, HTLV-1 infection was revealed as an independent risk factor for the progression of atherosclerosis.

Discussion

We found a significant, positive correlation in Max-IMT for the HTLV-1 positive group. Moreover, HTLV-1 positivity was extracted as an independent factor for the development of atherosclerosis.

An association between HTLV-1 and atherosclerosis has been reported [12, 13], and high-resolution B-mode ultrasound imaging, especially measurement of carotid IMT, has been validated as an indicator of vascular risk [26]. There is no radiation exposure to the patient and it is relatively inexpensive. PWV, a non-invasive clinical indicator of aortic stiffness [27], can also be used to predict cardiovascular events and identify hypertensive patients in the general population [28, 29]. HTLV-1 infection has been positively associated with atherosclerosis [30, 31].

We found that our HTLV-1 positive group had significantly higher Max-IMT and PWV values than the HTLV-1 negative group. Furthermore, as a result of adjusting for age, sex, smoking, BMI, SBP and PWV, HTLV-1 was found to be a significant independent factor of arteriosclerosis. Change in systemic inflammation has been seen in HTLV-1-infected patients, even in those who are asymptomatic [18]. Because HTLV-1 potentially causes atherosclerosis, this suggests that the progression of atherosclerosis is influenced not only by age but also by HTLV-1 persistence.

As with HIV [32, 33], both atherosclerosis and chronic HTLV-1 infection are disease states characterized by the presence of low-grade chronic inflammation. Atherosclerosis has also been associated with metabolic risk factors [16]. Recent studies have shown that viral and bacterial causes may be responsible for coronary artery disease and its restenosis after angioplasty. Infections have been linked to inflammatory cytokines, and these have been linked to factors that accelerate CVD. Other proposed associations include CMV, chlamydia pneumoniae, *Helicobacter pylori*, EBV, HIV and other infectious diseases [34].

Plasma levels of monocyte chemotactic protein-1 (MCP-1) are associated with risk factors for atherosclerosis [34, 35], and further experimental studies may help to further understand our results.

There are several limitations to this study. In carotid echo, the measurement results may be slightly affected by differences in evaluators. Although there was a broad age range, our participants tended to be of higher age (median age 63 years). Intervention for younger participants needs to be done to promote early detection of arteriosclerosis and disease prevention.

Conclusion

Our results indicate that HTLV-1 infection is causative of atherosclerosis and CVD. Routine cardiovascular monitoring of HTLV-1-infected patients, even asymptomatic carriers, is important. In this study, the HTLV-1 positive group showed significantly higher Max-IMT and PWV values than the HTLV-1 negative group. In addition, HTLV-1 positive was extracted as an independent factor for the development of atherosclerosis. These results suggest that HTLV-1 infection confers a high risk of atherosclerosis, although the reverse relation is possible, especially for the younger generations with HTLV-1. Careful attention should be paid to the early stages of the progression of atherosclerosis.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Written informed consent was obtained from all residents and patients included in this survey.

Author Contributions

Dr. Takeoka was the lead researcher and analyzed the data. Dr. Sagara assisted by doing laboratory testing for the HTLV-1 and supervised and helped design the study. Dr. Kashiwagi and Dr. Nabeshima supervised and helped design the study.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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