Seroepidemiology of Human T-Cell Lymphotropic Virus Type I Infection in Taiwan


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ABSTRACT

The epidemiological characteristics of human T-cell lymphotropic virus type I infection in Taiwan have been explored by an island-wide community-based survey, which was carried out among residents in 19 townships and metropolitan precincts randomly selected through stratified sampling. Serum specimens of 7278 healthy subjects were screened by enzyme-linked immunosorbent assay and confirmed by Western blot method. A total of 103 subjects showed positive or weak reactions by enzyme-linked immunosorbent assay, but only 35 of them were confirmed to be positive by Western blot analysis. The anti-human T-cell lymphotropic virus type I antibody positive rate was 4.81/1000. The seropositive rate increased with age in both males and females, and females had a greater seropositive rate than males for all the age groups. Aborigines and Hakka Taiwanese had higher seropositive rates than Fukien Taiwanese and Mainland Chinese. Those people with lower educational levels were found to be associated with higher anti-human T-cell lymphotropic virus type I seropositive rates.

INTRODUCTION

Since the first isolation and characterization of HTLV-I from cultured cells derived from individuals affected with T-cell malignancies (1), several studies have accumulated serological, epidemiological, and virological evidence strongly suggesting that HTLV-I is associated with certain types of human T-cell leukemia and lymphoma (2, 3). The development of serological assays for HTLV-I made studies on epidemiological characteristics of HTLV-I infections possible (4, 5). The anti-HTLV-I antibody-positive rates were reported to be the highest in southwestern Japan (6), Carribean basin (7), and parts of Africa (8). Although the virus was suggested to be of African origin and to have disseminated to endemic regions a long time ago (9), its world-wide distribution and possible transmission routes still remain to be delineated.

Taiwan locates closely to the southwestern Japan where HTLV-I and its associated T-cell malignancies are endemic. Taiwan had also been occupied by Japanese for 50 years, and there has been a great deal of migration flow and sociocultural interchanges between the two regions. It is thus worthwhile to examine the prevalence of HTLV-I infection in Taiwan. Although there were some preliminary studies on anti-HTLV-I antibody screenings in Taiwan (10, 11), those results should be interpreted with caution for the selection bias and the lack of information on age and sex distribution. In addition, methods of examination should be standardized, especially in the cases of international comparison and risk factor investigation.

This large-scale community-based study was carried out with following specific aims: (a) to estimate the prevalence rate of HTLV-I infection based on anti-HTLV-I antibody tests; (b) to elucidate epidemiological characteristics of HTLV-I infection; and (c) to explore possible risk factors associated with the HTLV-I infection.

MATERIALS AND METHODS

Study Population and Sample Selection. The total population in Taiwan Island, Penghu Islets, and Orchid Islet was chosen as the study population. The general population was first stratified according to ethnic characteristics and resident areas. Ethnicity was divided into 4 strata including aborigines, Fukien Taiwanese, Hakka Taiwanese, and Mainland Chinese whose parents were born in mainland China; their resident area was divided into 5 strata including northern Island, southern Island, western Island, eastern Island, and adjacent islets. As only a few Hakka Taiwanese lived in adjacent islets, there were a total of 19 strata in this study. One urban or rural township or metropolitan precinct was randomly selected from each stratum.

The study subject size to be sampled from each stratum was estimated as 400 given the conditions of a HTLV-I antibody-positive rate of 1% with a standard error of 5/1000. The study subjects were selected according to the following multistage random sampling method. A total of 5 villages were randomly selected from each stratum, and 5 neighborhoods were further randomly selected from each sampled village. Systematic sampling was used to select 6 households from each neighborhood. Altogether, there were 150 households included in each study township or precinct. All family members of sampled households were requested for their voluntary participations. In all, 7278 study subjects were recruited in this study.

Serum Collection and Questionnaire Interview. Public health nurses in local health centers of 19 studied townships and precincts were well trained as home visit interviewers. All study subjects were informed of the details of the study purposes, benefits, and possible risks by interviewers. After the consent of study subjects, interviewers collected blood specimens and information regarding possible risk factors related to HTLV-I infection from study subjects. A 10- to 15-ml blood sample was collected from each subject and serum specimens obtained were kept at −70°C till the laboratory examination.

A structured questionnaire was designed, pretested, and revised to obtain information on risk factors. Enquired informations included sociodemographic characteristics, familial history of leukemia/lymphoma and other cancers, medical and surgical history, and life-styles. All sociodemographic characteristics were further checked with records kept in Household Registration Offices where any event of birth, death, marriage, migration, and occupational change is mandatorily registered.

Laboratory Examinations of HTLV-I Infection. Serum samples were first screened by ELISA (12) and then confirmed by Western blot. ELISA were done using kits (Biotech Research Laboratories, Inc.) according to recommended procedures. The positive control average was between 0.700 and 1.000 at A405nm, and the negative control average was less than 0.100. When the values of the test serum average >50% of the positive control average were considered as positive, those values between 21 and 49% of the positive control average were considered a weak reaction, and values <20% of the positive control average were considered negative.

All of the serum samples with ELISA-positive or weak reactions were subjected to Western blot confirmation. Serum samples with positive Western blot confirmed were further subjected to enzyme-linked immunosorbent assay (ELISA) by kits (Biotech Research Laboratories, Inc.) and C-terminal anti-HTLV-I antibody protein to confirm seropositive rates. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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together with 85 randomly selected ELISA-negative serum specimens were further confirmed by Western blot. The test was carried out using assay kits [Diagnostic Biotechnology (Pte) Ltd., Singapore] according to recommended procedures. Both nonreactive and reactive controls were run with every batch of assay. The test serum was considered as positive on Western blot in the case with the presence of bands of "p19 and p24" or "p19, p21, and gp46".

Data Analysis and Statistical Methods. Only positive serum sample confirmed by Western blot was considered as seropositive for anti-HTLV-I antibody in the data analysis. Age-sex-adjusted rates calculated through direct adjustment using the world population in 1976 (13) as the standard population were used to compare seropositive rates among different groups. The increasing trend of age-specific seropositive rates was tested for its significance by the \( \chi^2 \) test for a linear trend (14), while the significance of the difference in age-sex-adjusted seropositive rates among comparison groups was tested by the Mantel-Haenszel summary \( \chi^2 \) test (15).

RESULTS

ELISA and Western Blot Results. Among 7278 serum specimens tested by ELISA, a total of 49 were found to be positive, while 54 had weak reactions. All of these 103 serum samples and 85 randomly selected ELISA-negative serum samples were further examined by Western blot. As shown in Table 1, 33 (67.3%) of the 49 ELISA-positive samples, 2 (3.7%) of the 54 samples with weak ELISA reactions, and none of the 85 ELISA-negative samples were Western blot positive. The overall seropositive rate against HTLV-I among the general population of Taiwan was estimated as 4.81/1000.

Age-Sex-specific Seropositive Rate. Age-sex-specific anti-HTLV-I antibody-positive rates of 7278 study subjects are shown in Table 2. The age of 4 female study subjects was not available. The age-sex-specific seropositive rates were found to increase with age in both males and females. The increasing trend of seropositive rate by age was statistically significant in both males and females at \( P < 0.01 \). The seropositive rate of anti-HTLV-I antibody was higher in females than males for all age groups. The higher the age, the greater was the sex difference in seropositive rates. The age-adjusted seropositive rate was significantly higher in females (4.80/1000) than in males (2.88/1000) based on the Mantel-Haenszel \( \chi^2 \) test.

Table 1 Western blot analysis of ELISA-reactive and nonreactive serum samples

<table>
<thead>
<tr>
<th>Western blot analysis*</th>
<th>Positive</th>
<th>Weak</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>33</td>
<td>2</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Negative</td>
<td>16</td>
<td>52</td>
<td>85</td>
<td>153</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>54</td>
<td>85</td>
<td>188</td>
</tr>
</tbody>
</table>

* Positive, (a) presence of both p19 and p24 bands or (b) presence of bands of p19, p21, and gp46; negative, neither of above conditions.

Table 2 Age-sex-specific anti-HTLV-I antibody-positive rates

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No. tested</th>
<th>No. positive*</th>
<th>Rate/1000</th>
<th>No. tested</th>
<th>No. positive</th>
<th>Rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>1043</td>
<td>0</td>
<td>0</td>
<td>979</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>20-39</td>
<td>885</td>
<td>2</td>
<td>2.26</td>
<td>1274</td>
<td>3</td>
<td>2.35</td>
</tr>
<tr>
<td>40-59</td>
<td>809</td>
<td>5.54</td>
<td>8.96</td>
<td>1006</td>
<td>18</td>
<td>1.76</td>
</tr>
<tr>
<td>60+</td>
<td>710</td>
<td>9.86</td>
<td>13.52</td>
<td>617</td>
<td>11.84</td>
<td>1.91</td>
</tr>
<tr>
<td>Total</td>
<td>3541</td>
<td>14</td>
<td>3.95</td>
<td>3733</td>
<td>21</td>
<td>5.63</td>
</tr>
</tbody>
</table>

* Four female cases whose age was not available were excluded from 7278 randomly selected study subjects.

Ethnicity-Residence-specific Seropositive Rate. Table 3 illustrates anti-HTLV-I antibody-positive rates in 19 ethnicity-residence strata. Generally speaking, aborigines and Hakka Taiwanese had higher seropositive rates than Fukien Taiwanese and mainland Chinese, while the rate was the highest in western Island and the lowest in adjacent Islets. However, the ethnic difference in seropositive rate was not consistent in different resident areas. The resident difference in the seropositive rate was not consistent in different ethnic groups either. Aborigines in Taiwan Island had a rather high seropositive rate, but those in Orchid Islet did not have any positive reaction. Hakka Taiwanese had significantly higher seropositive rates in northern and western Island, but there was no positive case in southern and eastern Island.

Educational Level and Seropositive Rate. Table 4 shows the age-sex-adjusted seropositive rates in different educational levels and resident areas. The age-sex-adjusted seropositive rate was significantly higher in the low educational level group, i.e., illiterate or elementary school graduates, than the high educational level group, i.e., junior high school graduates or above, regardless where study subjects resided. The age-sex-residence-
adjusted seropositive rate was 3 times higher in the low educational level group (10.35/1000) than the high educational level group (3.46/1000). Interestingly, among those who had low educational levels, residents of metropolitan precincts had a much higher positive rate than did those of other resident areas. On the contrary, among those with high educational levels, residents of metropolitan precincts and urban townships had positive rates lower than those of rural and aboriginal townships.

**DISCUSSION**

The quality and comparability of results obtained from various seroepidemiological studies depend on the representativeness of the study population, the method of subject sampling, the validity and reliability of serological examinations, the details of data analysis and result description. There have been several studies on seroepidemiological characteristics of HTLV-I infection in recent years (16–20). However, some of them did not specify details of the study population and some failed to provide prevalence by age, sex, and other pertinent characteristics. The HTLV-I-seropositive rate was reported to be 1.3% in Taiwan in previous studies (10, 19). Our previous screening test for HTLV-I antibody in 300 subjects, who visited our hospital for hematological and cancer treatments, by membrane fluorescence antibody in 1983 showed a positive rate of 1%.

The results of those studies were difficult to interpret and to compare for their small sample size, ill-defined population, biased selection, and/or inadequate method to determine the seropositivity. Both ELISA and Western blot method were used in this study, and only those specimens with positive reactions on Western blot were considered as seropositive. The prevalence rate was thus estimated as 4.81/1000 in Taiwan. The HTLV-I infection in the general population of Taiwan seems not as prevalent as that observed in the southwestern Japan and Okinawa Islets.

The HTLV-I-seropositive rate was observed to increase with age in this study. The result is consistent with those reported in previous studies done in Japan, Hawaii, and other countries. The age dependence of HTLV-I prevalence might result from the increased exposure to the virus as age increases and/or the long latency between infection and antibody response. Further investigation on the age dependence phenomenon, especially in familial aggregated cases, will differentiate the possibility of two alternatives. The HTLV-I-seropositive rate was also observed to be higher in females than in males in this study, especially in age groups of 40 or more. This female predominance of the HTLV-I-seropositive rate was also observed in Japan (6). Long-term follow-up of healthy seropositive cases will answer at least parts of the phenomenon.

The differences in the seropositivity among four ethnic groups and in different areas of the Island were inconclusive. This might due to the small effective sample size and low seropositivity. Cluster sampling rather than simple random sampling was used to select study subjects; therefore the effective sample size might be smaller than 400 as originally estimated and the standard error becomes larger. The small number of seropositive cases further reduces the power to detect such extrabinomial variation. However, there do exist some ethnicity-residence strata with higher seropositive rates. Comprehensive survey of these “hot spots” might shed light on the possible transmission routes of HTLV-I in a community.

A low educational level was found to be associated with a high HTLV-I-seropositive rate. The exploration of a possible explanation of the high infection rate in the low educational class will provide important information on the risk factors associated with the HTLV-I infection.

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