Heterosexually Acquired HTLV-III/LAV Disease (AIDS-Related Complex and AIDS)

Epidemiologic Evidence for Female-to-Male Transmission

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- Thirty-seven percent (15/41) of patients with human T-cell lymphotropic virus type III (HTLV-III) disease (acquired immunodeficiency syndrome [AIDS] or AIDS-related complex) sequentially evaluated at Walter Reed Army Medical Center, Washington, DC, acquired this infection from a partner(s) of the opposite sex. Demographic features of these 15 patients (ten males and five females) differed substantially from those for patients reported to the Centers for Disease Control. Heterosexual contact with partners who developed AIDS or who were at risk for AIDS was confirmed in six patients. The remaining nine patients had multiple (>50) heterosexual partners and/or sexual contact with prostitutes. The method of sexual activity did not appear to be related to disease acquisition; however, this study clearly demonstrated that receptive anal intercourse was not a requirement. The observations reported herein provide further epidemiologic evidence to support the occurrence of bidirectional heterosexual transmission (both male to female and female to male) of HTLV-III infection and disease.

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HUMAN T-cell lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) infection is the cause of a unique clinical syndrome recently recognized in the United States, the acquired immunodeficiency syndrome (AIDS). This virus is responsible for a variety of clinical syndromes, whose clinical presentation reflects the integrity of the T-helper cell population. We and others have shown that patients with chronic unexplained lymphadenopathy and persistent depletion of T-helper cells, termed "AIDS-related complex" (ARC), belong to the same spectrum of disease. See also pp 2059, 2089, 2129 and 2130.

Promiscuous homosexual males, intravenous (IV) drug abusers, hemophiliacs, and recent Haitian immigrants to the United States were recognized to be at the highest risk for AIDS. Subsequently, persons receiving multiple transfusions of blood or blood products, and infants of mothers in high-risk groups, were also found to be at risk. Previous observations also suggested heterosexual acquisition of AIDS by female sexual partners of male members of high-risk groups, and recently the frequent transmission of HTLV-III to wives of patients with ARC and AIDS was demonstrated. Herein we describe additional evidence for significant heterosexual transmission of HTLV-III infection by providing evidence for both male-to-female and female-to-male transmission of infection and disease.

PATIENTS AND METHODS

Patients having AIDS or ARC were evaluated and followed up by the Infectious Disease Service at Walter Reed Army Medical Center, Washington, DC. The ARC is defined as chronic lymphadenopathy with a duration of more than three months with nodules of at least 1 cm in diameter, involving two or more extranodal sites, and an absolute T-helper cell depletion (T-helper cell count of <400/cu mm) persistent for a minimum of six weeks. Cases of AIDS were identified among patients hospitalized with an opportunistic infection and meeting the case definition of AIDS. All patients were interviewed on multiple occasions by trained investigators to ascertain possible AIDS risk factors. Family members and/or acquaintances were interviewed when available. Any evidence for behavior characteristics suggestive of either homosexual activity, including asymptomatic rectal carriage of gonorrhea, or IV drug abuse (evidence of needle abuse) resulted in classification of individual as member of an appropriate risk group. Heterosexual contact was defined as oral-genital, vaginal, or rectal intercourse. Individuals were defined as having multiple heterosexual contacts if they had more than 50 different sexual partners over the past five years.

Mononuclear cells were obtained from heparinized whole blood by banding in Ficoll-Hypaque solution and were subtyped using fluorescently labeled Leu 1, Leu 2, and Leu 3 monoclonal antibodies and fluorescent antibody cell sorter. The lymphocyte population was gated between volume parameters to exclude macrophages.

Delayed hypersensitivity was determined as a clinical parameter assessing in vivo T-cell function. The test for anergy included intradermal skin testing with tetanus, mumps, Candida, and Trichophyton. Complete anergy was defined as an absence of a delayed hypersensitivity response to all four antigens. Partial anergy was defined as an intact delayed hypersensitivity response to only one of the four test antigens.

Heparinized whole blood (50 ml) was collected and processed within three to four hours. Mononuclear cells were collected by banding in Ficoll-Hypaque solution and treated for 48 hours with purified phytohemagglutinin (5 μg/ml). Mononuclear leukocytes were established in culture in growth media supplemented with 10% T-cell growth factor. The production of HTLV-III was monitored as release of extracellular reverse-transcriptase activity, and by electron microscopic examination, measurement of intracellular expression of viral proteins, and transmission to fresh human T lymphocytes or established T-cell lines as previously described.

Serum or plasma samples were tested for the presence of antibody to HTLV-III structural proteins by enzyme-linked immunosorbent assay and Western blot procedures as previously described. Antibody to hepatitis virus A and B was detected using radioimmunoassays. Cytomegalovirus serological testing was performed by complement fixation. Epstein-Barr virus serological testing was determined by immunofluorescence assay using immunoglobulin to viral capsid anti-
Table 1.—Demographic Features of HTLV-III* Disease Diagnosed at Walter Reed Army Medical Center, Washington, DC†

<table>
<thead>
<tr>
<th>Feature</th>
<th>With HTLV-III Virus (%)</th>
<th>Without HTLV-III Virus (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>87 (78)</td>
<td>83 (72)</td>
<td>170 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (22)</td>
<td>17 (18)</td>
<td>30 (10)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>43 (39)</td>
<td>41 (39)</td>
<td>84 (32)</td>
</tr>
<tr>
<td>Black</td>
<td>43 (39)</td>
<td>41 (39)</td>
<td>84 (32)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (16)</td>
<td>15 (16)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Haitian</td>
<td>0 (6)</td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>27 (34)</td>
<td>29 (34)</td>
<td>56 (30)</td>
</tr>
<tr>
<td>Range</td>
<td>24-35</td>
<td>19-48</td>
<td>19-48</td>
</tr>
</tbody>
</table>

*HTLV-III indicates human T-cell lymphotropic virus type III.
†Patients referred to Walter Reed Army Medical Center between July 1983 and May 1985, diagnosed with AIDS or ARC as described in the "Patients and Methods" section.

RESULTS

Forty-one sequential cases of HTLV-III disease (ARC/AIDS) were evaluated at the Walter Reed Army Medical Center. All patients were exposed to HTLV-III documented by either virus isolation and/or by detection of serum antibody against viral structural proteins. Demographic information and epidemiologic features of these 41 patients are summarized in Tables 1 and 2. In 15 (37%) of 41 patients with HTLV-III disease (ARC or AIDS), HTLV-III infection appeared to have been heterosexually acquired. This included ten males and five females. Exposure to HTLV-III was confirmed by virus isolation in 11 of these 15 patients, and all 15 patients demonstrated serum antibody to HTLV-III structural proteins by Western blot techniques.

More detailed demographic features of the 15 heterosexual cases are summarized in Table 3. From the information obtained, HTLV-III was most likely to have been acquired by recurrent heterosexual contact with a sexual partner with documented HTLV-III disease in three patients; heterosexual contact with a sexual partner who was a member of a high-risk group for AIDS (recent Haitian female immigrant, New York City bisexual male, and a New York City IV drug abuser) in three patients; and multiple heterosexual contacts including sexual contacts with prostitutes in the remaining nine patients. The number of different heterosexual partners over the past five years was more than 50 partners for eight of these patients and more than 100 partners for five of these patients.

The method of sexual activity did not appear to be unique in these patients. All 15 routinely engaged in vaginal-penile intercourse. In addition, none of the 15 regularly practiced oral-vaginal/oral-penile sexual activity. Only two individuals engaged in occasional insertional anal intercourse with their heterosexual partners. The five females all denied receptive anal intercourse.

Serological evidence of exposure to other sexually transmitted agents was determined in these patients. Two patients (13%) had evidence of previous exposure to T. pallidum. Seven of 15 had previous evidence of hepatitis B virus infection. Serological evidence of previous cytomegalovirus and Epstein-Barr virus infections were common (73% and 87%, respectively).

COMMENT

The heterosexual transmission of viruses is well documented. For example, the epidemiology of HTLV-III disease resembles that of hepatitis B virus, an agent clearly heterosexually transmissible." Also HTLV-I, another member of the HTLV family of retroviruses, has been demon-
strated to be horizontally transmitted from male to female in nonhuman primates and to be both vertically and horizontally transmitted in human family studies.11,12 In a similar manner, epidemiologic studies have suggested the acquisition of AIDS and ARC by heterosexual contact. For example, male-to-female transmission was supported by observation of AIDS developing in female sexual contacts of males with AIDS.13 Furthermore, the frequent transmission of HTLV-III among spouses of patients with ARC and AIDS demonstrates that recurrent heterosexual exposure is efficient for male-to-female HTLV-III transmission.14 In addition, recent reports from Africa support female-to-male transmission, demonstrating a male-to-female ratio for AIDS of 1:1:1, as well as the documentation of AIDS in spouses, common heterosexual contacts, and female prostitutes. As suggested in this study, prostitutes were probably exposed to HTLV-III by sexual exposure to HTLV-III-infected males, possibly bisexual males or males from endemic areas such as equatorial Africa. Concurrent use of IV drugs could also be a contributing factor in some instances. Prostitutes could serve as a reservoir for HTLV-III infection for heterosexually active individuals. Seroprevalence studies in certain prostitute populations support the mode of transmission implied in this study (M. Robert-Guroff, PhD, oral communication, September 1984). The acquisition of HTLV-III infection and AIDS by newborns of high-risk mothers further demonstrates the ability of females to transmit this virus and disease.

Heterosexual acquisition of HTLV-III disease was implicated in 15 of the 41 ARC or AIDS cases recognized at Walter Reed Army Medical Center, second only to the combined impact of homosexual-bisexual acquisition. Although military patients may be particularly reluctant to admit to certain risk behaviors, corroboration of patient information was obtained by interviews with family members and other acquaintances and by physical examination, including a rectal culture for gonorrhea, before including these patients in the heterosexual acquisition category. 

Demographic information on the 15 patients who contracted HTLV-III by heterosexual contact differs substantially from that for patients reported with AIDS to the Centers for Disease Control. For example, 33% are female (as opposed to 7%); 13% were white, 67% were black, and 20% were Hispanic (as opposed to 59% white, 25% black, and 14% Hispanic, respectively). Kapoosi's sarcoma, although easily diagnosed, was not present as an opportunistic process in any of the seven patients with heterosexually acquired AIDS. These patients also lacked evidence of active cytomegalovirus disease and asymptomatic rectal carriage of gonorrhea, and demonstrated a low prevalence of previous exposure to syphilis. These observations are consistent with nonhomosexual acquisition of HTLV-III infection.

The actual mechanism of transmission of virus and the relative efficiency for male-to-female and female-to-male transmission is not known; however, it is clear, from the cases reported herein, that receptive anal intercourse is not required for heterosexual HTLV-III transmission. The finding of infectious virus in lymphocytes isolated from semen supports male-to-female venereal transmission;15; however, the presence of virus and/or infection in female genital venereal excretions has not been reported. The isolation of infectious virus from saliva raises the possibility of nonvenereal sexual transmission through mucous membrane exposure to infectious virus. This means of transmission through intimate salivary exchange could contribute to the transmission of HTLV-III.

Originally, when AIDS was recognized in the homosexual community, both the degree of sexual activity and the geographic location were important co-risk factors. These same parameters should also be considered in the heterosexual community. An increased risk of HTLV-III disease acquired by heterosexual activity could be expected to be originally recognized in a sexually active population such as military personnel with sexual contacts in different parts of the world, although, the experience in a military population may not be representative of the general heterosexual community. Nonetheless, the demonstration of bidirectional sexual transmission of HTLV-III infection and disease has important implications. The ultimate impact that HTLV-III disease will have on the heterosexual community will be dictated by the extent of HTLV-III infection in the female partner of the infected individual, the natural history of the infection, and the presence or requirement of cofactors that modulate the development of disease. Currently, the extent of ARC and AIDS documented in the heterosexual community is limited; however, this is another population that should be considered at risk for both disease acquisition and HTLV-III transmission.

References