A Classification of HTLV-III Infection Based on 75 Cases Seen in a Suburban Community

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Abstract

Since 1981, 75 patients have been seen at our hospital with human T-cell lymphotropic virus type III (HTLV-III) infection. We have classified their clinical presentation into Groups 0 to 6. Groups 0 to 3 all have antibody to the M, 41,000 protein of HTLV-III. Group 0 has no evident disease (9 patients), Group 1 has lymphadenopathy with or without exaggerated infection (16 patients), Group 2 has persistent lymphadenopathy with chronic hepatitis B surface antigenemia or profound hypergammaglobulinemia (7 patients), Group 3 has oral candidiasis with or without lymphadenopathy (7 patients). In Group 4 are acquired immunodeficiency syndrome (AIDS) adults or children (32 patients). Group 5 is a special classification for immunocompromised patients. Group 6 patients have lymphomas and Mr 41,000 protein antibody. Four children were classified separately. Three patients in Group 3 developed Group 4 disorders (AIDS). Four patients in Group 4 developed Group 6 disorders. HTLV-III infection spread in families (8 of 36), all from infected mothers to children. In 17 sexual partners, 6 were found to be infected. Five of 6 infected partners were homosexuals. We saw an inordinate number of HIV+ infants also presented with severe intracranial defects, one with microcephaly and one with cranial calcifications and lucency. HTLV-III is spreading with alarming speed.

In 1978 severe opportunistic infections with associated recently acquired severe immunodeficiency (AIDS) began to appear in homosexual patients, intravenous heroin abusers, Haitians, hemophiliacs, patients receiving blood transfusion, and children of Haitian mothers and heroin addicts. AIDS has been spreading in alarming numbers throughout the United States and now in many parts of the world. This disorder of immunity appears to be due to a steady depletion of the T-helper cell population which ultimately leads to the development of frequently fatal opportunistic infections. Recently a retrovirus, now called HTLV-III, has been discovered which appears to be responsible for AIDS. The growth of this virus in a T-cell leukemic line clone (H9) has resulted in the production of large amounts of HTLV-III. The availability of this virus has led to the development of adequate serological tests to study the epidemiology of this virus. What has been immediately apparent is that while the case definition of AIDS has been an extremely useful indicator of the spread of this virus, it is only one of a variety of clinical manifestations of HTLV-III infection, which also includes persistent diffuse adenopathy (10) and recently aggressive non-Hodgkin’s lymphomas (11). It is the purpose of this study to delineate the spectrum and epidemiology of HTLV-III induced disorders as they occurred in our community.

Materials and Methods

North Shore University Hospital is a 600-bed community hospital situated approximately 32 miles outside of New York City. Our hospital services a relatively wealthy community which has only a small population of Haitians, heroin addicts, intravenous drug abusers, or homosexuals. Since the first description of AIDS we began to track this disorder in patients admitted to our hospital and seen in our clinics. Since generalized lymphadenopathy was also described as an “AIDS” related disorder we also tracked this disorder. In addition patients in risk groups for AIDS in our hospital were examined for possible aberrant medical illnesses which might be new. Families of AIDS patients and, whenever possible, sexual partners of these patients were also examined for any evident illness. Serum was obtained for future study.

Serological Studies

All sera were tested for antibody to HTLV-III using the Western blot method described previously (8). Patients entered in this study either had AIDS as defined by criteria previously described (2) or else they had antibody to at least the p41 HTLV-III protein. Some patients also had antibodies to other defined HTLV-III antigens.

T-Cell Markers

T-lymphocyte subpopulations were identified by indirect immunofluorescence using commercially available monoclonal antibodies (OKT3, OKT4, OKT8, and OKT11; Ortho Diagnostic Systems, Raritan, NJ).

HTLV-III Defined Illnesses

All patients in Groups 0 to 3 must be seropositive as defined above. They can then be grouped as follows:

Group 0. Patients who are seropositive but who on physical examination have no palpable LAD or any evident significant infections. These patients are functioning normally but may have T-cell abnormalities, moderately increased globulins (not greater than 2500 mg of IgG/ml), or neutropenia.

Group 1a. Patients with LAD involving any two noncontiguous chains of nodes from the posterior cervical, axillary, postauricular, epitrochlear, or inguinal area. These patients are asymptomatic and free of any exaggerated infection.

Group 1b. These patients have LAD as defined in Group 1a but in addition have exaggerated infections, including severe tinea versicolor of the skin, extensive molluscum contagiosum, prolonged pityriasis rosea, severe tinea cruris, recurring condyloma accuminata, extensive
secondary syphilis, or prolonged CMV infection with constant shedding of virus in urine or semen.

Group 2a. These patients have LAD with or without infection but in addition have persistent hepatitis B surface antigen positive.

Group 2b. These patients have LAD without infection but in addition have profound hyper-IgG gammaglobulinemia of greater than 2500 mg/mL.

Group 3. These patients have oral candidiasis either without evident prior antibiotic usage or which persists for 2 weeks or longer after antibiotics have been discontinued. These patients need not have LAD.

Group 4. These patients have AIDS as defined by the criteria of the Centers for Disease Control. They need not have antibody to p41.

Group 5. These patients have antibody to p41 and also have underlying neoplastic disease requiring chemotherapy. In addition they have an opportunistic infection as defined in the Centers for Disease Control criteria for AIDS.

Group 6. These patients have developed lymphoma of any type, angioimmunoblastic adenopathy, angioimmunoblastic sarcoma and/or refractory anemia with excess blasts. In patients who have severe T helper cell depletion of less than 150 cells, Western blots may have to be repeated at increased serum concentration to bring out the p41 antibody.

Childhood HTLV-III Disease

This classification is somewhat more difficult to make. These children must be less than 13 years old. They must also have antibody to at least p41. Group 4 conforms to the criteria utilized by the Centers for Disease Control (12) and also includes children with lymphocytic interstitial pneumonitis as well as other opportunistic infections. In addition any one of a unique group of congenital brain diseases, including anencephaly, microcephaly, and/or severe intracranial calcifications in children less than 4 months old (in the absence of evidence for cytomegalovirus infection, rubella, or toxoplasmosis) also qualifies a child for Group 4. It is rare for children to be hepatitis B carriers. Similarly they do not appear to get the same types of infections as do adults. For this study we will merely describe illnesses that do not fall into Group 4.

Results

A total of 75 patients with HTLV-III infection have been detected at our institution since January 1980. Our first patient was recognized in July 1981. From April 1983 to November 1984 a large increase in Group 4 cases has occurred. Similar epidemiology has been seen in Groups 0 to 3. The distribution of risk factors in Groups 0 to 4 is shown in Table 1.

Distribution of Patients in Groups. Nine patients were in Group 0, 6 patients were in Group 1a, and 10 presented with Group 1b disease. Five Group 1b patients had prolonged cytomegalovirus infection. Two patients with CMV converted their HTLV-III serology with the onset of CMV disease. Two had severe and prolonged infectious mononucleosis, one had severe secondary syphilis with meningitis, one had severe primary herpes simplex with many facial lesions as well as stomatitis, and one had extensive tinea versicolor with large plaques on his skin.

Three patients had Group 2a disease including one girl who had transfusion related LAD. She was found to have profound hyperglobulinemia with a monoclonal gammopathy. Four patients had Group 2b disease, and in all these cases patients had persistent splenomegaly. One of these patients developed HTLV-III antibody after having two separate open heart operations to treat severe endocarditis. This patient was an intravenous drug abuser as well. Seven patients presented with Group 3 disease. Two did not have LAD. One of these patients had recurrent herpes simplex perirectal infection and one had severe molluscum contagiosum.

Twenty-six patients presented with Group 4 (AIDS) disease. Ten children were found to be infected. Six of these had Group 4 disease.

Relationship to Absolute T-Helper Numbers. The average number of T-helper cells per cm² was 674 (n = 12; range, 1330 to 450) in Groups 1a and 1b, 346 (n = 7; range, 77 to 500) in Groups 2a and 2b, and 228 (n = 7; range, 50 to 1090) in Group 3.

Epidemiology of Infection in the Household and in Sexual Partners. Table 2 defines the extent of spread of HTLV-III disease in families. Spread was almost exclusively through sexual contact or from mother to child. In two siblings ages 5 and 7 years HTLV-III infection occurred possibly postnatally from their mother who had AIDS. There is, however, some possibility that there was child sexual abuse present in this particular family. It is to be noted that different manifestations of HTLV-III infection occurred in each family or sexual pair.

Transition Syndromes. Three patients in Group 3 developed Group 4 disease. Four patients in Group 4 developed Group 6 disease. One patient developed a central nervous system lymphoma and three developed lymphoma in other areas. Two of these patients also had Kaposi's sarcoma.

Unusual Features of Our Epidemic. We have witnessed an inordinate incidence of HTLV-III infection from transfusions. Four of 29 ultimate Group 4 patients and one of the remaining 46 other patients developed disease secondary to blood transfusion. All Group 4 patients received blood during surgical procedures performed in New York City in 1981.

Our ten childhood cases are of interest. Six children had Group 4 disease. Four children had different presentations. One child had recurring bacterial infections associated with oral and perianal candidiasis. One child was entirely asymptomatic but had profound abnormalities in T-cell function. Her sibling was more immunologically normal but had lymphadenopathy. A fourth child had extensive adenopathy. He had hemophilia and had received cryoprecipitate at birth to control an intracerebral hemorrhage. Two children in Group 4 presented with striking neurological disorders characterized in one by extensive intracranial lacunae and associated fatal Pneumocystis pneumonia and in another by microcephaly and intracranial calcifications. In all cases the mother had evidence of HTLV-III infection.

Table 1

<table>
<thead>
<tr>
<th>Risk groups</th>
<th>AIDS cases</th>
<th>Group 0 to 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homosexuals</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Addicts</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Caribbean</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Transfusion</td>
<td>4</td>
<td>1</td>
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<tr>
<td>Children of addic</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hemophiliacs</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No risk</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>43</strong></td>
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AIDS is spreading nationwide and worldwide with alarming vigor. In this study we propose a new classification which assumes that AIDS is but one aspect of HTLV-III infection. The cornerstone of this classification is the presence of antibody to the p41 protein, which appears to be the most sensitive and specific marker of this virus. Inherent in this classification is the supposition that there is a progressive decrease in T-helper cell number as one moves from Group 1 to Group 4. Group 0 is more difficult to define because it may contain totally asymptomatic patients who have immunodeficiency. In our community although we have seen 32 AIDS cases, 43 other patients have been found to be infected with HTLV-III. Clearly there are flaws in our detection system; nonetheless we can estimate that for every one Group 4 (AIDS) case there are at least 1.3 other HTLV-III infected cases in other groups. If we use the current statistics which tell us that there are at least 6000 cases of AIDS in the United States, we can assume that there are an additional 7800 HTLV-III infected individuals as well. This we believe must be a gross underestimate of the total spectrum of HTLV-III infections. Nonetheless the time has come to start to count these other HTLV-III disorders if we are going to develop strategies to control the spread of this virus.

This classification also gives us some insight into the biology of this virus. If one strain can produce Group 1 disease and another Group 4 disease then vaccine strategists would try to first produce vaccine against strains producing Group 4 or Group 6 disease. Unfortunately in the family studies which we performed, if we assume that the same strain of virus infects other family members or sexual partners, then it appears that one strain can produce a spectrum of illnesses. This variability in outcome produced by one virus is not surprising. It is, however, going to make it more difficult to create satisfactory vaccines because a series of strains will have to be incorporated into one vaccine.

It is not yet clear if there is progression from one group to another with time. Thus far it has been shown that patients with lymphadenopathy associated with candidiasis clearly progress to Group 4 disease (13). In addition in our study four patients with Group 4 disease progressed to Group 6 disease. Nonetheless we would not be surprised if some patients can present with Group 6 disease as an initial manifestation of HTLV-III infections. A recent study by Ziegler et al. (11) shows that there has been an alarming epidemic of aggressive lymphomas arising in homosexuals. The seroepidemiology of this group to HTLV-III will be of great interest. It will also be important to study lymphomas in order to discover how this virus contributes to the degree of malignancy. If these tumors are related in some way to HTLV-III then they should be counted in national statistics on the spread of this virus. A registry of these cancers must be established.

This classification is also useful if we are to recognize the extent of spread of virus via transfusion. It is via transfusion induced cases in Groups 0 to 3 that virus may spread outside of known risk groups. It is clear from viral studies already performed that antibody positivity is synonymous with the presence of retrievable virus from blood or from other organ sources (1). Even Group 0 patients are potentially as infectious as Group 4. The alarming serology surveys which suggest that as many as 57% of homosexuals (14) and 64% of hemophiliacs may be infected (15) bodes a frightening prognosis for control of this disease.

By attempting to create disease grouping we are really trying to turn attention to other possible clinical manifestations of HTLV-III infection. We can no longer afford not to count opportunistic infections caused by HTLV-III induced immunodeficiency but occurring in patients also immunocompromised by treatment for neoplastic disease as part of the "AIDS" epidemic (16). These patients have received the bulk of our blood supply. If we do not count them in national statistics we may overlook an important group of transfusion induced disorders. This is why we add Group 5 to the classification.

Finally by focusing our attention on other possible syndromes of HTLV-III infection we show that in children this virus may be associated not only with childhood AIDS but also with the potential for producing congenital malformation of the brain. This adds a whole new dimension to the problems this virus may create.

At the present time these groupings may need more refinement. The time has come for some uniform nomenclature which will be useful to describe the spectrum of HTLV-III infection so that precise studies can be carried out to define the natural history of this viral disorder. We hope that this study provides some framework on which a more solid nomenclature can be established.

References

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