Clinical Spectrum of HTLV-III in Humans

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Abstract

We have studied the clinical and laboratory manifestations of infection with human T-cell lymphotropic virus type III in various epidemiological cohorts. The spectrum of infection ranges from an asymptomatic but apparently contagious carrier state to severe immunodeficiency with opportunistic infections and neoplasms. Study of virus structure-function relationships and host response to viral infection in hosts with different clinical manifestations should provide strategies for therapeutics and vaccine development as well as enhance our understanding of the biology of human retroviruses.

Introduction

It is the role of the clinical investigator to act as a bridge between phenomenology and pathophysiology. By meticulous descriptions of clinical presentations of human disease, questions are generated regarding the mechanisms wherein pathological changes occur in the affected host. Efforts over the past 4 years have been initially to describe the clinical manifestations of AIDS and related disorders (ARC) (1-3). This has involved clinical evaluation of symptomatic and asymptomatic individuals at risk epidemiologically for the syndrome. Although most of our clinical population at risk are homosexual or bisexual men, we have also had the opportunity to study certain transfusion recipients, hemophiliacs, Haitians, i.v. drug abusers, and transplant recipients. We have sought to understand the typical manifestations of AIDS and ARC but have also made special efforts to study those "exceptions to the rule" because we believe careful description of atypical occurrences of AIDS and ARC may yield special insights into the pathophysiology of the disorders.

It is now overwhelmingly clear that HTLV-III is the primary etiological agent in AIDS and ARC (4-9). In collaboration with Gallo and coworkers (10) we initially studied mainly homosexual and bisexual men with AIDS (defined as Kaposi's sarcoma and/or life-threatening opportunistic infections according to criteria from the Centers for Disease Control).

Materials and Methods

Three assays have been used to detect antibody to HTLV-III related antigens, an enzyme linked immunosorbent assay (ELISA), Western blot, and indirect membrane immunofluorescence (6, 7, 11, 12). The designation of a true seropositive is made on the basis of demonstrating antibody by Western blot to either the M, 24,000 core protein or the M, 41,000 envelope-associated glycoprotein of HTLV-III. We have studied at the New England Deaconess Hospital 70 patients with Centers for Disease Control-defined AIDS, 100 patients with ARC, and 200 healthy homosexual men without clinical symptoms. Virus culture for HTLV-III was performed as described previously (5, 13).

Results

The ELISA assay detected antibody in 45% of AIDS patients, 82% of ARC patients, and 92% of healthy homosexual men who were antibody positive by Western blot. The seroprevalence among these groups is 98% antibody positive among AIDS patients, 92% among ARC patients, and 23% among healthy homosexual men (10). Thus ELISA is a reasonable screening test for asymptomatic individuals at risk for AIDS as well as for ARC patients in terms of "true positives" by Western blot; it is probable that the failure of ELISA to detect antibody among AIDS patients relates to the decrease in antibody titre which occurs as AIDS patients enter the terminal phases of their illness. Interestingly the membrane immunofluorescence assay, which is relatively rapid and easy to perform, has an excellent correlation with true positives by Western blot. Indeed in studies done collaboratively with Barin et al. (14) there was only a single patient with ARC who was antibody negative by immunofluorescence assay and proved to be antibody positive using radioimmunoprecipitation. The fluorescence assay appears to be detecting antibodies to envelope-associated glycoproteins which are expressed on the surface of the HTLV-III infected H-9 cells that are used as targets in the assay. Probably the high M, 120,000 glycoprotein which appears to be a transmembrane protein in HTLV-III infected cells is the most immunogenic antigen in patients with various disease manifestations after HTLV-III infection. In studies done with Barin et al. (14) antibody to this transmembrane antigen is found in all patients. This is of interest since it appears that the first antigen that elicits an antibody response is the M, 24,000 core antigen and only later after infection is there an antibody response that is detectable to the M, 41,000 envelope-associated glycoprotein. Even in the earliest phases after infection when only antibody to the core antigen is detected by Western blot, there appears to be antibody directed against the high molecular weight transmembrane protein detected by radioimmunoprecipitation. We are currently following patients prospectively and studying titre and distribution of antibody to different HTLV-III related antigens in order to determine whether such antibody might be of prognostic importance, i.e., whether individuals who appear to have been infected with HTLV-III and have not yet developed opportunistic infections or neoplasms might have a certain antibody profile while those who have progressive clinical disease might have a different profile. Furthermore changes in such antibody profile may be an early indication of conversion from an asymptomatic prodromal state to clinical disease.

ARC generally presents as prolonged generalized unexplained lymphadenopathy involving two noncontiguous lymph node sites other than the inguinal area. There are a number of other manifestations of HTLV-III infection in humans distinct from...
generalized lymphadenopathy. We have studied high risk individuals (mainly homosexual and bisexual men) with isolated unexplained leukopenia, isolated unexplained thrombocytopenia, or recurrent herpes zoster. Men with one or several of these manifestations have been studied and all are antibody seropositive for HTLV-III. Unexplained pancytopenia or an isolated cytopenia is a frequent manifestation of HTLV-III infection in high risk individuals. It is important for the hematologist to be aware of such manifestations. The bone marrow is nondiagnostic in such persons showing adequate precursors of platelets, RBC, and WBC (although there may be some element of maturation arrest in the myeloid series). Recurrent herpes zoster, although it does not qualify in the criteria for AIDS set forth by the Centers for Disease Control, is certainly an opportunistic infection in high risk individuals and indicates immune deficiency on the basis of HTLV-III infection.

Perhaps the most striking observation regarding HTLV-III infection is the large number of individuals who are able to chronically carry virus without any clinical manifestations. This is most evident in studies on high risk blood donors whose blood products have apparently transmitted AIDS (13, 15). Most of these individuals do not develop clinical AIDS. We have identified several chronic carriers of HTLV-III who are asymptomatic but have apparently transmitted the disease. We have studied a heterosexual woman who developed AIDS after having regular vaginal intercourse with a Haitian man (16). This man denied homosexual activity, i.v. drug abuse, or receipt of blood products. He chronically carries HTLV-III in peripheral blood and sheds the virus in his saliva. It is now 3 years since he apparently transmitted the virus to this woman and yet he has no clinical manifestations of the disease except for some mild lymphadenopathy. We have also identified a blood donor who apparently transmitted AIDS via his blood products nearly 6 years ago (15). The recipient of his packed RBCs developed transfusion associated AIDS about 3 years after receipt of blood products. This man is of particular interest since he has virtually no clinical manifestations of immune deficiency and has normal total lymphocyte number, normal T-cell subsets, normal skin test reactivity to recall antigens, normal proliferative responses to lectins and antigens, and yet carries HTLV-III in his blood and sheds the virus in his saliva. Furthermore our study of the transfusion recipient indicated that she had only been infected with HTLV-III and had not been infected with cytomegalovirus, Epstein-Barr virus, hepatitis B virus, or adenosivirus. Our inference from this study is that HTLV-III may act as the sole viral agent in induction of immunosuppression in AIDS. There has been considerable speculation that cofactors, particularly other viruses such as cytomegaloviruses and Epstein-Barr virus, are either important or necessary in "priming" the host to HTLV-III infection. Although it is difficult to state that these herpes viruses are not important, it is clearly possible to develop AIDS after infection with only HTLV-III (15). We have also studied a Haitian family in Boston in which two children have severe opportunistic infection and qualify as pediatric AIDS. The mother is entirely asymptomatic but is positive for HTLV-III antibody and is presumably transmitting the virus to her children either in utero or in the peripartum period.

These studies are more than clinical anecdotes. It is extremely difficult to discern the event and source of exposure to HTLV-III among sexually active gay men and i.v. drug abusers since such individuals have multiple opportunities for exposure during sexual contacts and use of contaminated needles, respectively. Furthermore the high background prevalence of herpes virus infections, particularly cytomegalovirus, among homosexual men makes it nearly impossible to study the role of such viruses since both cases and asymptomatic controls show evidence of prior or current infection. We have though studied the relationship between HTLV-III antibody seropositivity and sexual practices among homosexual and bisexual men (10). In a seroepidemiological study in Boston among asymptomatic homosexual men who had a known sexual contact with a man who later developed AIDS, it appeared that individuals who did not engage in anal receptive intercourse had a significantly lower prevalence of antibody to HTLV-III compared to those who did engage in such sexual practice. This led us to conclude that if antibody to HTLV-III is a good marker for infection, then receptive anal intercourse may be one of the highest risk sexual practices for homosexual men with respect to transmission of the virus. It is possible that trauma to the rectal mucosa allows contact of the virus which is carried in semen with the target circulating T4 lymphocytes. Saliva is also occasionally used as a lubricant in anal intercourse among homosexual men and with our identification of HTLV-III in saliva we propose that this might be a second route of transmission of the virus during anal intercourse. Nonetheless we found it surprising that only 60% of the cohorts who had had sexual contact with an AIDS patient were antibody positive for HTLV-III. This led us to study the possibility that individuals might be infected with HTLV-III and yet remain antibody seronegative for prolonged periods of time (17). We are currently studying individuals who epidemiologically are at extremely high risk for HTLV-III (known sexual contact with an AIDS patient and multiple anonymous contacts, particularly those involving receptive anal intercourse) and have identified five individuals who are antibody seronegative and virus positive for HTLV-III. Such individuals are asymptomatic, have normal titres of antibody to other viruses such as varicella, and have normal T-cell subsets and skin test reactivity to recall antigens, and three of five have entirely normal physical examinations (the other two have minimal enlargement of lymph nodes in cervical and axillary areas). One homosexual whose regular sexual partner had AIDS has been seronegative for 12 months and virus positive for at least 7 months. We are currently studying these individuals for potential seroconversion. In addition in collaboration with Gallo et al.4 we have undertaken a molecular analysis of the viral isolates from these persons to see if there might be structure-function relationships that explain the clinical phenomenology. Finally to determine if these isolates are transmissible we are infusing chimpanzees with plasma from antibody negative, virus positive individuals in conjunction with Dreesman, Essex, et al.4

One of the most dramatic new clinicopathological occurrences in AIDS is the development of an unexplained dementia among some of the patients. Central nervous system dysfunction may occur due to a variety of infectious or neoplastic processes, including toxoplasmosis, progressive multifocal leuкоencephalopathy, herpes simplex, and lymphoma. A subset of individuals with encephalopathy in the setting of AIDS have had no explanation for their loss of cortical function. In collaboration with Shaw et al. (18) we have studied the brains of AIDS patients with dementia due to identified infections and those without clear evidence of infection. In four of the five cases we have studied there was a consistent pathologic change in the cerebral cortex which was recognized as an unusual glial proliferation. This change was characterized by a proliferation of large round cells, sometimes with abundant eosinophilic cytoplasm, containing one or several large nuclei. The nuclei were usually large and hyperchromatic, with prominent nucleoli. The cells were usually arranged in a sheet-like pattern and often contained numerous long processes. The glial reaction was usually confined to the cerebral cortex and was most marked in the supragranular layers. In some cases the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate. In one case there was a severe gliosis involving the entire cerebral cortex, with many of the cells showing a granular or foamy appearance. In a few cases, the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate. In one case there was a severe gliosis involving the entire cerebral cortex, with many of the cells showing a granular or foamy appearance. In a few cases, the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate. In one case there was a severe gliosis involving the entire cerebral cortex, with many of the cells showing a granular or foamy appearance. In a few cases, the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate. In one case there was a severe gliosis involving the entire cerebral cortex, with many of the cells showing a granular or foamy appearance. In a few cases, the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate. In one case there was a severe gliosis involving the entire cerebral cortex, with many of the cells showing a granular or foamy appearance. In a few cases, the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate. In one case there was a severe gliosis involving the entire cerebral cortex, with many of the cells showing a granular or foamy appearance. In a few cases, the cells were also present in the subcortical white matter. The glial proliferation was often accompanied by a mild lymphocytic infiltrate.

3 J. E. Groopman, R. C. Gallo, et al., manuscript in preparation.
4 Dreesman, M. Essex, et al., manuscript in preparation.
explanation. Our studies indicate that HTLV-III is capable of infecting nonlymphoid cells in brain, is found by molecular hybridization techniques diffusely throughout brain, and is not uniformly found in all AIDS patients. It appears that individuals with unexplained dementia have a high rate of HTLV-III infection of brain whereas those studied who had central nervous system toxoplasmosis, progressive multifocal leukoencephalopathy, etc., did not have HTLV-III in brain. This is strong circumstantial evidence that HTLV-III may result in an encephalopathy.

Discussion

Continued clinical efforts have helped us chart out future laboratory directions in our study of HTLV-III infection in humans. An antigen assay is clearly important to determine readily how many individuals may be infected with HTLV-III and yet not mount an antibody response. Until such an antigen assay is available we will continue to perform virus isolation. It is our impression that significant numbers of individuals may be infected with HTLV-III and yet not mount an antibody for months to perhaps even years. Such an impression is important to verify in terms of the current efforts to screen blood products for HTLV-III using laboratory directions in our study of HTLV-III infection in humans. We are currently studying on a molecular basis in collaboration with Gallo et al. the structure of paired isolates of HTLV-III, i.e., one isolate which was epidemiologically transmitted to a second person. This is most readily accomplished in our studies of heterosexuals who were monogamous and sexually transmitted the virus as well as in transfusion-associated AIDS. It is quite probable that there is a larger family of human T-cell lymphotropic retroviruses which cause a variety of malignant and immunosuppressive diseases in humans. We are applying the current level of technology with respect to cell culture and molecular biology to the study of tissues that derive from individuals with T-cell lymphoproliferative disorders as well as persons with aplastic anemia. It is probable that the insights derived from the study of HTLV type III in AIDS in conjunction with knowledge on HTLV types I and II will equip us with the ability to identify further retroviral pathogens in humans.

References

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