Unique Pattern of HTLV-III (AIDS-related) Antigen Recognition by Sera from African Children in Uganda (1972)

Carl Saxinger, Paul H. Levine, Andy Dean, Gunhild Lange-Wantzin, and Robert Gallo

Laboratory of Tumor Cell Biology (C. S., R. G.) and Clinical Epidemiology Branch (P. H. L.), National Cancer Institute, Bethesda, Maryland 20205; Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark [G. L.-W.]; and International Agency for Research on Cancer, Lyon, France [A. D.]

Abstract

Of 75 sera collected in the West Nile district of Uganda over a 1-year period between 1972 and 1973, 50 (66%) had antibody reactivity to human T-cell lymphotropic virus subgroup III (HTLV-III) at low titer levels. Sera were initially screened by HTLV-III enzyme linked immunosorbent assay and sera with values less than normal mean + 2 SD were removed from testing. The remaining sera were tested for positivity by an amplified Western blotting procedure which incorporated a three-layer immunoperoxidase procedure. Immunoglobulin reactive with HTLV-III or of HTLV-II itself but existing in a population acclimated to its presence. It further suggests a likely African origin of HTLV-III.

Introduction

Since the isolation and establishment of highly efficient cell clones producing the HTLV-III virus (1, 2), data have rapidly accumulated linking the virus with AIDS, its associated prodrums, and risk groups. Both AIDS and HTLV-III/LAV are known to occur among homosexual or bisexual men, intravenous drug abusers and their infants, female sexual partners of men with the syndrome, and patients with hemophilia (3–7). AIDS as a separate disease entity was initially recognized in 1981, coinciding with the new and steadily increasing prevalence of antibody to the virus in these populations (8–10). Prospective studies have confirmed that those with antibodies are most likely to develop AIDS (11, 12). In contrast normal blood donors have antibodies to the virus at a much lower level (13).

Where and how the disease arose are presently open questions but several observations are consistent with an African origin (14). AIDS cases have been described, although only recently, among black Africans (15–18) and among Europeans who had a history of travel in Africa (19, 20). Most of the African cases have been from Central Africa, Zaire, and Rwanda. These cases appear to be typically positive for HTLV-III/LAV (21). Although no AIDS cases have been reported from Uganda, cases of Kaposi’s sarcoma in homosexual men with AIDS were documented in 1971 (22, 23). Earlier studies from our laboratory and others indicated that HTLV-I occurs with high frequency in regions of central Africa (24) and that closely related retroviruses were present in many species of Old World monkeys (25). A major point of interest was the high prevalence of HTLV-I antibodies in Ugandan children from the West Nile district, collected in 1972 and 1973 from isolated subsistence farming regions. This group with little exposure to international travelers provided an opportunity to study the prevalence of HTLV-III in a natural, relatively undisturbed ecological environment. Several important observations have emerged from this study (26): (a) the high prevalence of antibodies reactive with HTLV-III (or relative) suggests a long history of the virus within the populations; and (b) the data also suggest that the natural history of infection, immunity, and disease in this population may be different from others showing a high prevalence of the virus.

Materials and Methods

The Ugandan sera tested were primarily from clinically healthy donors randomly selected as controls for Burkitt’s lymphoma cases on the basis of age, sex, and community. All sera were collected between August 1972 and July 1973 (27). The mean age of the patient population was 6.4 years (27). Sera from this collection were tested for antibodies recognizing HTLV-III in two stages. First all sera were tested by indirect ELISA for quantitative levels of IgG binding to disrupted HTLV-III virions coated onto the wells of microtiter plates (28). HTLV-III virions were produced in high quantity by specific clones from a permissive human neoplastic T-cell line (1). Test results were transformed into a normal distribution as described previously (24, 26) and indexed to a standard normal serum. All sera with normalized values exceeding a cutoff level of the mean + 2 SD (determined from 356 normal blood donors) were then selected for further testing by Western blotting (13). Visualization of IgG was performed using a modified peroxidase-antiperoxidase reagent (26). Sera from Danish normal volunteer blood donors were collected by Professor Henning Sorensen at the Rigshospitalet, University Hospital of Copenhagen Blood Bank, serving the Copenhagen area. HTLV-III antibody positive sera were obtained from asymptomatic homosexual males from Denmark also from the Copenhagen area. Titration data were obtained from serial dilutions of a test sample in the standard ELISA protocol. The data were analyzed using the equation in reciprocal form for molecular binding (25). The slope for the regression line where X = serum dilution and Y = inverse absorbance (values of 1/A > 25 were excluded) was determined and the general equation for a straight line was used to solve for X = titer. The titration end point was the value of Y for a 1/20 dilution of standard normal serum.

Results

From the group of 75 Ugandan sera tested for reactivity with HTLV-III by ELISA, 50 of 55 which exceeded the 2 SD limit were...
confirmed by their recognition of specific HTLV-III viral bands for an overall positivity rate of 66% (26). The most prominent reactions were with antigens with molecular weights of 76,000, 41,000, and 24,000. Less frequently recognized antigens were with molecular weights of 64,000, 59,000, and 18,000. These values coincided with the previously described molecular weights of HTLV-III antigens recognized by sera from AIDS or AIDS-risk patients (29). The distribution of titer values of HTLV-III positive sera is shown in Table 1. Clearly most of the Ugandan serum titers fell within the range of 100–1,000. The geometric mean titer was 295 and coefficient of variation (performed on log [titer]) was 52%. Mean titer was 601.

Discussion

The combination of HTLV-III antibody prevalence and pattern of antigen recognition found in these Ugandan subjects is unique and totally different from that found in any other previously described normal or AIDS-risk populations. Antigen recognition by the Ugandan sera was directed toward multiple viral components in the same manner found with AIDS-risk sera. However, HTLV-III titers of the Ugandan sera were two to three orders of magnitude lower than usually found in AIDS-risk groups. Although occasional normal donors appear to possess antibody reactivity within the titer range of 100–1,000 toward HTLV-III, these antibodies have characteristically recognized only the M, 18,000 or M, 24,000 viral proteins.

Until now it has generally been considered that the high prevalence of HTLV-III antibodies is associated with high risk for the AIDS disease. Whether or not AIDS is endemic in regions of Uganda is presently unanswered. However, it seems reasonable to believe, given the high prevalence rate of HTLV-III viral antibodies in Ugandan children, that the origin of HTLV-III or a highly related virus within this population is not recent and that the natural history of virus infection, immunity, and disease can be different in some populations. As with many other infectious diseases host responsiveness may vary between severe and subclinical and may depend on the age of initial exposure.

If recent reports of AIDS in Central Africa which have suggested that the AIDS disease is newly evolved and spreading (16) are correct, then it is of great concern to determine which of the various host or virus related factors may be responsible. For example it would be important to know whether the current spread of AIDS was due to a spread of HTLV-III or a related virus from nonsusceptible or immune to susceptible populations or to a molecular change in the AIDS agent. In this regard our samples were taken from a sparsely populated rural subsistence farming environment where AIDS is not known to occur while the recent spread in African AIDS appears to be in more densely populated urban environments including heterosexual populations (30). However, it is still possible that our assay has detected host responses to a virus closely related to the AIDS-related HTLV-III but which lacks pathologic activity. Such a virus might have been the predecessor from which the pathogenic AIDS-related HTLV-III arose by mutation, or it might be a new member of the human HTLV retrovirus family. We have shown previously that the immunological cross-reactivity between HTLV-I or HTLV-II and HTLV-III in our assay is practically nonexistent (26). Therefore isolation and molecular characterization of the agent from healthy individuals as well as from patients with AIDS from African populations such as the one described here will be necessary to compare it with the virus causing AIDS. In particular, infants and young children should be examined, for if the agent detected in our present studies is HTLV-III then it is of the utmost importance to determine the factors contributing to survival in these virus endemic populations.

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References


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