CONTINUING MEDICAL EDUCATION

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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"AIDS is knocking on the doors of Asia", according to Dr Jonathan Mann, Director of the AIDS control programme of the WHO. Though AIDS has barely surfaced in Asia and a few cases have been reported in India and the continent as a whole, involves mainly foreigners, female prostitutes and people who have had blood transfusions abroad. This may actually represent only a tip of an epidemic iceberg, as many more people are infected than the cases reported. Yet because AIDS is occurring later in Asia than in other continents, we can benefit from the knowledge gained at a heavy price elsewhere.

It was in June 1981, that the Centres for Disease Control, Atlanta (USA) learnt of an increased incidence of opportunistic infections especially *Pneumocystis carinii* pneumonia(PCP),[1] and rare malignancies especially Kaposi's sarcoma (KS),[2] concentrated amongst homosexual men, mainly from the cities of New York, Los Angeles, San Francisco and California. It soon became apparent that these were the first cases of a new epidemic disease of extraordinary morbidity and mortality, the basis of which was a profound defect in cellular immunity, subsequently termed as Acquired Immune Deficiency Syndrome (AIDS). The causative agent of AIDS was later found to be a Type-C retrovirus, Human T-Cell Lymphocytotropic retrovirus (HTLV-III), also called as Lymphadenopathy-Associated virus (LAV) or AIDS-associated retrovirus (ARV). The virus has a predilection for helper T-lymphocytes (designated as OK T4, CD-4 or Leu 3 cells) and virtually converts the T cells from a lymphocyte to a HTVL-III virus factory ultimately reducing their number and interfering with their function, thereby producing a state of cellular immuno-deficiency, which clinically manifests as rare opportunistic infections or unusual malignancies. Despite this state of cellular immuno-deficiency, humoral immunity to the virus develops in the form of antibodies, which have no protective value, but are invaluable in the diagnosis. Like other retroviruses, however, the result of HTLV-III infection may be variable. The virus may remain in a state of latency, or replicate without producing any clinical feature or may produce an overt disease.

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Definition

AIDS has been defined empirically as a disease with features of immune deficiency in the form of opportunistic infections like *Pneumocystis carinii* pneumonia and tumours like Kaposi's sarcoma in patients less than 60 years of age having absence of the known causes of immuno-deficiency like lympho-reticular malignancy and immuno-suppressive therapy.[4]

In addition, Centres for Disease Control have added the following criteria for diagnosis of AIDS :

(a) In individuals more than 60 years of age, histopathologically confirmed Kaposi's sarcoma with seropositivity for HTLV-III virus.

(b) In children less than 13 years of age, histopathologically confirmed interstitial pneumonitis.

Epidemiology

Patients with AIDS have now been reported from 127 countries, spread over all the continents. Till 31 July 1987, 55,396 cases were reported worldwide with 9 cases from India and 160 cases from 18 countries in Asia. The epidemic at present appears to be taking place in USA and Western Europe. Other regions significantly affected are central Africa and Haiti.[5-6] Individuals who are at high risk of contracting HTLV-III infection are :

(a) Almost all the initial patients and the majority (71-78%) of newly discovered patients of AIDS in USA and Europe are homosexually acquired. Kaposi's sarcoma is also seen mainly in this group.[6-8]

(b) Being female seems to confer relative immunity to AIDS and male to female ratio is about 20 : 1. However, heterosexual transmission of the disease is not uncommon. In fact in Africa, the victims are over-whelmingly heterosexuals.

(c) Intravenous drug abusers without a history of homosexual activity constitute about 13% of all cases.[9]

(d) Haitians with no history of male homosexual activity or I V drug abuse constitute about 6% of all cases. They have an increased incidence of *Mycobacterium tuberculosis* and toxoplasmosis infections.[10]

(e) Haemophiliacs who are treated with lypholized factor VIII concentrate (but not those treated with cryoprecipitate) are at higher risk. There are also patients with AIDS but without haemophilia where the only recognizable risk factor was blood transfusion. These observations suggest that the causative agent is transferable by blood or blood products.[11]

(f) Mother to foetus or mother to offspring transmission of virus can occur during pregnancy, labour and during caesarean section or breast feeding.[12]

According to a recent estimate, as many as five million individuals are infected with the virus in USA alone, though only 1% of these have the full-blown disease. How many out of these cases are ultimately going to develop the disease, is a point of conjecture, though it is feared by various workers that it may be anything between 50-90%. It is believed that something triggers the activity of the virus, but as yet the factors necessary to create the right conditions for activity remains a mystery.[13] However, some of the known factors are male sex,[14] prematurity,[15] repeated antigenic stimulation in the form of rectal intercourse or contaminated needles,[16] other viral infections and other factors which suppress the immune system (drugs, surgery).

Clinical features

The incubation period of the disease ranges from 6 months to 5 years and possibly longer. Currain et al in their study of 18 patients of transfusion associated AIDS (TA-AIDS) observed a mean incubation period of 27.5 (15-57) months.[17]

Approximately two thirds of the persons infected with the HTLV-III virus and followed up for at least five years have no evidence of ill health. It is not known what risk of disease those individuals face beyond five years. The remaining one third develop illness varying in severity from ARC (AIDS-related complex) to AIDS. Thus, the disease forms a spectrum ranging from a mere sero-positivity for virus called as pre-AIDS to ARC to clinical AIDS.

Pre-AIDS

These are infected individuals in the incubation period who are seropositive for HTLV-III virus. They in addition, have OK T4 :

OK T8 ratio less than one and elevated levels of serum P2-microglobulins.[18]

AIDS related complex (ARC)

These are infected sero-positive individuals who also have, (a) lymphadenopathy, fever, weight loss and diarrhoea, (b) no opportunistic infection or malignancy, and (c) inverted OK T4 : OK T8 ratio.

Progressive generalized lymphadenopathy[10] which may antedate AIDS by about 18 months, is suggested by following features : (i) lymphadenopathy greater than 1.0 cm, present for at least three months and in at least two extragenital sites. (ii) absence of an acute illness at the onset of lymphadenopathy. (iii) no history of drugs, immunisation, or other factors known to cause lymphadenopathy.

Clinical AIDS

This is characterized by the evidence of immuno-deficiency in the form of absolute persistent decrease in OK T4 lymphocytes with relatively normal OK T8 lymphocytes; opportunistic infections and/or malignancy especially Kaposi's sarcoma.

Malignancies : Kaposi's sarcoma, Burkitt like lymphomas, squamous cell carcinoma of tongue or anus and intracranial lymphomas are the usual tumours. Kaposi's sarcoma (KS) is the most common malignant tumour seen. It occurs alone in about 25% cases and in association with PCP in another 10%. KS in AIDS is like the African form of disease with high incidence of visceral involvement.[20] Early skin lesions are inconspicuous, looking like Campbell de Morgan spots, which later involve the mucous membranes and internal organs.

Opportunist infections : These infections are frequent, multiple and recurrent and it is usually difficult to predict the infecting agent by clinical and radiological examinations alone.

(a) Pulmonary infections : The classical triad offever, dyspnoea and widespread interstitial infiltrations on chest X-ray may be modified, and sometimes the chest X-ray may be normal. Though the parasites are occasionally seen in expectorated sputum, the diagnosis usually depends on fibreoptic bronchoscopy or open lung biopsy. Other infections include typical or atypical mycobacteriosis, cryptococcosis and cytomegalovirus (CMV) infections.

(b) GIT infections : Thrush (*Candida albicans*) is common. Herpes simplex and CMV may cause oesophagitis and deep painful ulcerations around the mouth and anus. Gut colonisation with coccidian parasite, cryptosporidium, is the most common infection in active homosexuals causing severe debilitating diarrhoea and associated weight loss.

(c)CNS infections : Toxoplasmosis commonly presents as a space-occupying lesion and a trial of empirical therapy is justified. If no clear improvement occurs within a few days, brain biopsy should be done to differentiate potentially treatable infections (tuberculosis, cryptococcosis) from non-infective causes (lymphomas). Encephalopathy and dementia, due to AIDS has also been described.

(d) Eye infections : CMV retinitis may lead to blindness.

(e) Disseminated infections : Disseminated *Mycobacterium avium intercellulare*, CMV infections and septicemia due to *Salmonella* and *Cryptococcus* are quite common.

Skin manifestations : Patients with AIDS and ARC are prone to skin disorders other than Kaposi's sarcoma. Most patients suffer from more than one skin disorder at a time. These include chronic ulcerative genital herpes simplex herpes zoster, muco-cutaneous candidiasis, fungal infections, chronic pyoderma and seborrhoeic dermatitis. Immune complex vasculitis, folliculitis and xeroderma have recently been

added to this list.[20] Some early warning skin signs have been described viz chronic acneiform folliculitis, a florid beard and neck impetigo and severe fungal infections.[21-24]

Immunopathology

HTLV virus appears to be having cytotropism for OK T4 cells. Host defence in the form of cytotoxic/suppressor T cells (OKT8) tries to destroy the infected OKT4 cells.[25] The increasing number of OKT8 cells and diminishing OKT4 cells result in the loss of cell mediated immunity, as confirmed by loss of cutaneous delayed hypersensitivity both to recall and new antigens, and poor response to in vitro mitogens such as phytohaemagglutinin. B cell abnormalities include, polyclonal activation of B cells, resulting in a polyclonal rise in IgG.

Laboratory findings

1. Lymphopenia (1500/cmm) is the simplest screening test for suspected AIDS. OKT4 : OKT8 ratio is reversed (normal 1.5-2.0).

2. Serological tests for herpes simplex virus, CMV, Epstein Barr and syphilis are frequently positive.[26]

3. Immunoglobulins (IgG and IgA), and circulating immune complex levels are elevated.

4. The screening test for HTLV-III antibody is an enzyme linked immunoassay (ELISA) test (sensitivity 97-98%, specificity 93-99%). A positive ELISA test should be confirmed by a Western blot antibody test or immunosorbent assay test. Weakly positive ELISA tests may be false positive due to hepatitis, alcoholic liver disease, malaria or in multiparous women.

5. Detection of virus has been possible in 36-48% of advanced AIDS patients.

Management

Till date, no therapy has resulted in restoring the immune function of an AIDS patient. The treatment comprises of specific therapies for the opportunistic diseases and malignancies in each individual case.

1. Attempts at immune reconstitution with interferon, interleukin-2, thymic hormones and bone-marrow transplantation have met with minimal success. High dose I V immunoglobulin (300 mg/kg, biweekly) has inhibited or reversed immunologic deterioration in some patients.[26,27]

2. Antiviral drugs like suramin, riboviran, HPA-23 and azidothymine have been tried, but with little success.[26]

3. KS in some patients has responded to epipodophyllotoxin, but high dose human leucocyte interferon ($25\text{-}30 \times 10^6$ units/ml^2) has also shown encouraging results.[27]

4. PCP responds well to co-trimoxazole but some patients may require pentamidine.

5. Toxoplasmosis responds well to a combination of pyrimethamine and sulphadiazine.

Future

Multiple approaches to vaccine development are currently in progress. These include, purification of selected envelope components from the disrupted virus and the production of envelope proteins by recombinant DNA technology, using a HTLV IV virus or a simian virus called STLV III, which affects monkeys in Africa. No attempts are being made to develop a live attenuated or whole virus inactivated vaccines, because of the hypothetical potential for nucleic acid to integerate into the host cell DNA. The main problem in finding an AIDS vaccine is due to the characteristic of the HTLV-III virus to undergo antigenic drift following minor mutations, resulting in alterations of the molecular structure of its protein coat. Therefore, until a common antigen is found from multiple strains of the HTLV-III virus, a vaccine may not be possible. WHO officially estimates that a vaccine will not be ready for at least five years. Even when a vaccine is developed, it is unlikely to be effective against individuals who are already infected. Curative therapy will be even more

difficult, because HTLV-III is a latent virus, and right now no drugs are available which affect the latent form.

Till we develop combative measures to control this devastating epidemic, prevention is the only tool to contain the disease. AIDS is not highly contagious in the usual sense of the term; it spreads in a pattern similar to the hepatitis B virus infection via the body secretions, contaminated needles and blood products. The general procedures designed for the care of patients with hepatitis B virus infection will be appropriate. In addition, re-establishment of social codes and re-acceptance of condoms will go a long way in controlling not only AIDS, but also other sexually transmitted diseases.

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