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VIROLOGY AND IMMUNOLOGY OF HIV INFECTION

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Acquired Immune Deficiency Syndrome (AIDS) is now a major health problem. Till the end of 1991, about 5 lakh AIDS cases have been reported in the world; but the true figure may be about 2 to 10 times more. It is estimated that more than 40 million AIDS patients will be there by the year 2000 AD. In western countries, the infection curve is plateauing. However in Asia and Africa, the steep rise in new infection still continues. Providing health care for these individuals is likely to further strain the already severely strained resources of developing countries. In certain areas of Africa, it is reported that only grand parents and infants are available; the young adult population has been completely wiped out by the AIDS. In some North Eastern states of India, about 50% of population has already become seropositive. All over India taken together the seropositivity is 1/200. In certain areas of this country, the seropositivity is 1/20 in high-risk groups. The International Conference on AIDS held in Vancouver in 1996 declared that India has the largest number of HIV infected people.

In 1981, a cluster of *Pneumocystis carinii pneumonia* in Los Angels and another cluster of Kaposi's sarcoma in NewYork were reported. A new disease was thus identified. A virus was isolated from these cases. It was originally named as Human T-cell Lymphotropic Virus (HTLV III), which was later re-named as Human Immunodeficiency Virus (HIV).

HIV belongs to retrovirus group. The genetic materials is made up of a single stranded RNA. By means of the enzyme reverse transcriptase, the RNA is copied into DNA. This provirus is usually integrated into the host DNA by the action of viral integrase. Retroviruses do not replicate in non-dividing cells. In the quiet T cell, the virus is not integrated and replicated. The major genes on the RNA strand are LTR (Long terminal repeat), Gag, Pol, Env and another LTR in that order. In addition, there are 6 regulatory genes named as Vif, tat, rev, nef, vpr and vpu.

The Gag gene produces a protein with a molecular weight of 53,000 and is named as p-53. During viral maturation, p-53 is further processed into p-17, p-24, p-7 and p-6 which are then incorporated as core proteins. Pol gene produces the reverse transcriptase enzyme (p-56) and an Endonuclease or Integrase (p-31) and a Protease (p-11).Azathioprine will inhibit the activity of reverse transcriptase and is therefore useful to decrease virus multiplication. Env

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gene produces envelope glycoprotein, gp-160 initially, which is further processed into gp-120 and another transmembrane component of gp-41. The gp-120 is very important for the entry of virus into the susceptible cells. Attachment of the virus to the host cell is mediated through a receptor mechanism. CD4 molecules on the target cells act as receptors for gp -120 present on the envelope of the virus. Then gp41, the transmembrane protein produces fusion between viral envelope and host membrane. Thus the viral RNA is internalised into the host cell. The CD4 molecules on the target cells act as receptors for gp - 120 present on the envelope of the virus.

Then gp41, the transmembrane protein produces fusion between viral envelope and host membrane. Thus the viral RNA is internalised into the host cell. The CD4 molecules are present on the surface of T-helper cells and therefore helper cells receive the maximum attack of HIV. Moreover, macrophages, monocytes, Langerhan's cells, follicular dendritic cells and glial cells are also susceptible to HIV entry and propagation. In fact, monocyte/macrophage system acts as the reservoir of HIV infection.

Different strains of HIV have been reported, based on the antigenic composition of the virus envelope proteins. HIV-1 and HIV-2 are important types. Both types are seen all over the world, including India. Combined HIV-1 and HIV-2 detection kits are marketted so that detection of the latter will not be missed.

Following the entry of the virus inside the body, it takes come time to multiply and causes an immune reaction. This is called the window period, which may be a few weeks to a few months.

During this time, the virus is replicating inside the cells; the viral capsid antigen p24 can be detected in the blood during this time. However, this test is available only in selected research institutions, and therefore, for practical purposes, the window period could not be detected.

Then antibodies against the virus are seen in the circulation. This is called seropositiveness. This is identified by taking the serum of the patient and doing a latex agglutination test or an ELISA (enzyme linked immunosorbent test). Antibodies against envelope glycoproteins are detected by these methods. They are cheap and so are very useful as screening tests. However they may show some false positive tests. Therefore all the ELISA positive sera are to be tested by immunoblot or western blot for confirmation. Here, virus antigens are separated by electrophoresis and blotted to a nitrocellulose membrane, over which patient's serum is added. If antibodies are present, they stick over the antigen and could then be identified by colour reaction.

About 10% of seropositive individuals develop AIDS disease within 5 years; about 50% of seropositive persons develop the disease within 10 years; and 90 % within 15 years. All seropositive individuals irrespective of whether they have disease manifestations or not, can transmit the disease.

The crux of the problem is the destruction

of T-helper (CD4) cells. They are destroyed by the viral lytic process. The host immune response against HIV infected target cells by cytotoxic T-lymphocytes or by ADCC (antibody dependent cell mediated cytolysis) could also lyse the infected T-helper cells. The HIV infected cells shed gp-120 molecules into circulation, which is then bound to CD4 positive normal T-helper cells. These helper cells though uninfected, are now coated with gp-120, and become perfect targets for immunoreactive T-killer cells. This over enthusiastic cell - mediated immune response is the most important cause for immune suppression.

T - helper cells play a pivotal role in generation of cell mediated as well as antibody - mediated immune reactions. Therefore when T-helper cells are decreased in number, all the following immune effector arms are paralysed. a) cytotoxic T - cells, b) antibody dependent complement mediated cytolysis c) antibody dependent cell - mediated cytolysis d) macrophage system - all these are suppressed. When immunity is depressed, commensal pathogens can thrive well in tissues, causing disease manifestations.

Tat protein (p16) is produced under the influence of the Tat gene of the virus. It inhibits antigen-induced proliferation of lymphocytes, which is one of the improtant causes of immune depression. Tat protein also has a stimulatory effect on the growth of Kaposi's sarcoma cells. The incidence of Kaposi's sarcoma is 1000 fold increased in HIV infection.

In the seropositive asymptomatic individuals, the presence of antibodies are to a certain extent protective. Absolute count of T-helper cells will be less than 400/cu mm, but more than 300 in these individuals. (normal value is more than 400/cu mm). In such persons, circulating immune complexes composed of HIV antigen + antibodies are also detected.

When the disease manifestations are started, the T-helper count decreases to 200 or still low. The antibody titre starts to decrease. The antigen, especially the core protein, P-24, starts to rise. A rapid rise of serum beta 2 macroglobulin (B2M) is also associated with such a downhill clinical course. In the last stages, the immune system is so weak that antibody secreting cells are destroyed and patient may become seronegative.

Recently, it is noted that the degree of wasting at the later stages of the disease is independent of the immediate cause of infection. This tissue depletion could be arrested or reversed by nutritional support.

All infants born to seropositive women are seropositive at birth; these are the maternal antibodies entering to the fetal circulation. These passive antibodies will disappear over the next 6 months in uninfected children. There is no easy test for diagnosis of HIV infection at birth. Intrauterine infection occurs in about 30% cases. Transmission of HIV through breast milk is possible, but rare. The nutritional advantage and the emotional satisfaction provided by breast feeding far outweigh the small potential risk of HIV infection through breast feeding. Therefore breast feeding is recommended in infants born of seropositive mothers. There is no need to separate the child from the mother.

Against this pessimistic background, encouraging results have already been obtained in animal experiments, using the whole inactivated virus and boosting with the V3 loop of the gp120. Trials are also running with recombinant gp160 also. About 15 candidate vaccines are in the early stages of human trials. But it may take another 10 years to perfect an efficient vaccine.

Never before has so much been done in such a short time with regard to one disease. Within a short span of 10 years, the virus is identified, isolated, studied in great details; a simple detection method is now available and vaccines are under trial. Therefore there is hope amidst the very bleak present situation.