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Meningitis

Meningitis is inflammatory involvement of the meninges. Meningitis may involve the dura called pachymeningitis, or the leptomeninges (pia-arachnoid) termed leptomeningitis. The latter is far more common, and unless otherwise specified, meningitis would mean leptomeningitis. Pachymeningitis is invariably an extension of the inflammation from chronic suppurative otitis media or from fracture of the skull. An extradural abscess may form by suppuration between the bone and dura.

Further spread of infection may penetrate the dura and form a subdural abscess. Other effects of pachymeningitis are localised or generalised leptomeningitis and cerebral abscess.

Leptomeningitis, commonly called meningitis, is usually the result of infection but infrequently chemical meningitis and carcinomatous meningitis by infiltration of the subarachnoid space by cancer cells may occur. Infectious meningitis is broadly classified into 3 types: acute pyogenic, acute lymphocytic (viral, aseptic) and chronic (bacterial or fungal).

Acute Pyogenic Meningitis

Acute pyogenic or acute purulent meningitis is acute infection of the pia-arachnoid and of the CSF enclosed in the subarachnoid space. Since the subarachnoid space is continuous around the brain, spinal cord and the optic nerves, infection spreads immediately to whole of the cerebrospinal meninges as well as to the ventricles.

ETIOPATHOGENESIS. The causative organisms vary with age of the patient:

1. Escherichia coli infection is common in neonates with neural tube defects.

2. Haemophilus influenzae is commonly responsible for infection in infants and children.

3. Neisseria meningitidis causes meningitis in adolescent and young adults and is causative for epidemic meningitis.

4. Streptococcus pneumoniae is causative for infection at extremes of age and following trauma.

CLINICAL FEATURES

Acute bacterial meningitis is a medical emergency. The immediate clinical manifestations are fever, severe headache, vomiting, drowsiness, stupor, coma, and occasionally, convulsions. The most important clinical sign is stiffness of the neck on forward bending.

Chronic (Tuberculous and Cryptococcal) Meningitis

There are two principal types of chronic meningitis—one bacterial (tuberculous meningitis) and the other fungal (cryptococcal meningitis). Both types cause chronic granulomatous reaction and may produce parenchymal lesions. Tuberculous meningitis occurs in children and adults through haematogenous spread of infection from tuberculosis elsewhere in the body, or it may simply be a manifestation of miliary tuberculosis.

Less commonly, the spread may occur directly from tuberculosis of a vertebral body. Cryptococcal meningitis develops particularly in debilitated or immunocompromised persons, usually as a result of

haematogenous dissemination from a pulmonary lesion. Cryptococcal meningitis is especially an important cause of meningitis in patients with AIDS.

Typhoid (Enteric Fever)

The term enteric fever is used to describe acute infection caused by Salmonella typhi (typhoid fever) or Salmonella paratyphi (paratyphoid fever). Besides these 2 salmonellae, Salmonella typhimurium causes food poisoning.

PATHOGENESIS

The typhoid bacilli are ingested through contaminated food or water. During the initial asymptomatic incubation period of about 2 weeks, the bacilli invade the lymphoid follicles and Peyer's patches of the small intestine and proliferate.

Following this, the bacilli invade the bloodstream causing bacteraemia, and the characteristic clinical features of the disease like continuous rise in temperature and 'rose spots' on the skin are observed.

Immunological reactions (Widal's test) begin after about 10 days and peak titres are seen by the end of the third week. Eventually, the bacilli are localised in the intestinal lymphoid tissue (producing typhoid intestinal lesions), in the mesenteric lymph nodes (leading to haemorrhagic lymphadenitis), in the liver (causing foci of parenchymal necrosis), in the gall bladder (producing typhoid cholecystitis), and in the spleen (resulting in splenic reactive hyperplasia).

MORPHOLOGIC FEATURES

The lesions are observed in the intestines as well as in other organs.

1. INTESTINAL LESIONS. Grossly, terminal ileum is affected most often, but lesions may be seen in the jejunum and colon. Peyer's patches show oval typhoid ulcers with their long axis along the length of the bowel, (c.f. tuberculous ulcers of small intestine, described above).

The base of the ulcers is black due to sloughed mucosa. The margins of the ulcers are slightly raised due to inflammatory oedema and cellular proliferation. There is never significant fibrosis and hence fibrous stenosis seldom occurs in healed typhoid lesions. The regional lymph nodes are invariably enlarged.

2. OTHER LESIONS.
   Besides the intestinal involvement, various other organs and tissues showing pathological changes in enteric fever are as under: i) Mesenteric lymph nodes—haemorrhagic lymphadenitis. ii) Liver—foci of parenchymal necrosis. iii) Gallbladder—typhoid cholecystitis. iv) Spleen—splenomegaly with reactive hyperplasia. v) Kidneys—nephritis. vi) Abdominal muscles—Zenker's degeneration. vii) Joints—arthritis. viii) Bones—osteitis. ix) Meninges—Meningitis. x) Testis—Orchitis.

Leprosy

Leprosy or Hansen's disease (after discovery of the causative organism by Hansen in 1874), was first described in ancient Indian text going back to 6th Century BC, is a chronic non-fatal infectious disease affecting mainly the cooler parts of the body such as the skin, mouth, respiratory tract, eyes, peripheral nerves, superficial lymph nodes and testis. Though the earliest and main involvement in leprosy is of the

skin and nerves but in bacteraemia from endothelial colonisation or by bacilli filtered from blood by reticuloendothelial system, other organs such as the liver, spleen, bone marrow and regional lymph nodes are also involved. Advanced cases may develop secondary amyloidosis and renal disease, both of which are of immunologic origin.

Causative Organism

The disease is caused by Mycobacterium leprae which closely resembles Mycobacterium tuberculosis but is less acid-fast. The organisms in tissues appear as compact rounded masses (globi) or are arranged in parallel fashion like cigarettes-inpack.

M. leprae can be demonstrated in tissue sections, in split skin smears by splitting the skin, scrapings from cut edges of dermis, and in nasal smears by the following techniques:

1. Acid-fast (Ziehl-Neelsen) staining. The staining procedure is similar as for demonstration of M. tuberculosis but can be decolourised by lower concentration (5%) of sulphuric acid (less acid-fast).

2. Fite-Faraco staining procedure is a modification of Z.N. procedure and is considered better for more adequate staining of tissue sections.

3. Gomori methenamine silver (GMS) staining can also be employed.

4. Molecular methods by PCR.

5. IgM antibodies to PGL-1 antigen seen in 95% cases of lepromatous leprosy but only in 60% cases of tuberculoid leprosy.

Mode of Transmission

Leprosy is a slow communicable disease and the incubation period between first exposure and appearance of signs of disease varies from 2 to 20 years (average about 3 years). The infectivity may be from the following sources:

1. Direct contact with untreated leprosy patients who shed numerous bacilli from damaged skin, nasal secretions, mucous membrane of mouth and hair follicles.

2. Materno-foetal transmission across the placenta.

3. Transmission from milk of leprosy patient to infant.

Classification

Lepromatous type representing low resistance; and

Tuberculoid type representing high resistance.

Clinical Features

The two main forms of leprosy show distinctive clinical features:

1. Lepromatous leprosy:

i) The skin lesions in LL are generally symmetrical, multiple, slightly hypopigmented and erythematous macules, papules, nodules or diffuse infiltrates. The nodular lesions may coalesce to give leonine facies appearance.

ii) The lesions are hypoaesthetic or anaesthetic but the sensory disturbance is not as distinct as in TT.

2. Tuberculoid leprosy:

i) The skin lesions in TT occur as either single or as a few asymmetrical lesions which are hypopigmented and erythematous macules.

ii) There is a distinct sensory impairment.

Tuberculosis

Tissue response in tuberculosis represents classical example of chronic granulomatous inflammation in humans.

CAUSATIVE ORGANISM

Tubercle bacillus or Koch's bacillus (named after discovery of the organism by Robert Koch in 1882) called Mycobacterium tuberculosis causes tuberculosis in the lungs and other tissues of the human body. The organism is a strict aerobe and thrives best in tissues with high oxygen tension such as in the apex of the lung. Out of various pathogenic strains for human disease included in Mycobacterium tuberculosis complex, currently most common is M. tuberculosis hominis (human strain), while M. tuberculosis bovis (bovine strain) used to be common pathogen to human beings during the era of consumption of unpasteurised milk but presently constitutes a small number of human cases. Other less common strains included in the complex are M. africanum (isolated from patients from parts of Africa), M. microti, M. pinnipedii and M. canettii. A nonpathogenic strain, M. smegmatis, is found in the smegma and as contaminant in the urine of both men and women.

MODE OF TRANSMISSION

Human beings acquire infection with tubercle bacilli by one of the following routes:

1. Inhalation of organisms present in fresh cough droplets or in dried sputum from an open case of pulmonary tuberculosis.

2. Ingestion of the organisms leads to development of tonsillar or intestinal tuberculosis. This mode of infection of human tubercle bacilli is from self-swallowing of infected sputum of an open case of pulmonary tuberculosis, or ingestion of bovine tubercle bacilli from milk of diseased cows.

3. Inoculation of the organisms into the skin may rarely occur from infected postmortem tissue.

4. Transplacental route results in development of congenital tuberculosis in foetus from infected mother and is a rare mode of transmission.

TYPES OF TUBERCULOSIS

Lung is the main organ affected in tuberculosis. Depending upon the type of tissue response and age, the infection with tubercle bacilli is of 2 main types:

A. Primary tuberculosis

B. Secondary tuberculosis.

A. Primary Tuberculosis

The infection of an individual who has not been previously infected or immunised is called primary tuberculosis or Ghon's complex or childhood tuberculosis. Primary complex or Ghon's complex is the lesion produced in the tissue of portal of entry with foci in the draining lymphatic vessels and lymph nodes.

The most commonly involved tissues for primary complex are lungs and hilar lymph nodes. Other tissues which may show primary complex are tonsils and cervical lymph nodes, and in the case of ingested bacilli the lesions may be found in small intestine and mesenteric lymph nodes.

The incidence of disseminated form of progressive primary tuberculosis is particularly high in immunocompromised host e.g. in patients of AIDS.

B. Secondary Tuberculosis

The infection of an individual who has been previously infected or sensitised is called secondary, or post-primary or reinfection, or chronic tuberculosis.

The infection may be acquired from: endogenous source such as reactivation of dormant primary complex; or exogenous source such as fresh dose of reinfection by the tubercle bacilli.

Secondary tuberculosis occurs most commonly in lungs in the region of apex. Other sites and tissues which can be involved are tonsils, pharynx, larynx, small intestine and skin. Secondary tuberculosis of other organs and tissues is described in relevant chapters later while that of lungs is discussed here.

Secondary Pulmonary Tuberculosis

The lesions in secondary pulmonary tuberculosis usually begin as 1-2 cm apical area of consolidation of the lung, which may in time develop a small area of central caseation necrosis and peripheral fibrosis. It occurs by haematogenous spread of infection from primary complex to the apex of the affected lung where the oxygen tension is high and favorable for growth of aerobic tubercle bacilli.

Microscopically, the appearance is typical of tuberculous granulomas with caseation necrosis. Patients with HIV infection previously exposed to tuberculous infection have particularly high incidence of reactivation of primary tuberculosis and the pattern of lesions in such cases is similar to that of primary tuberculosis i.e. with involvement of hilar lymph nodes rather than cavitary and apical lesions in the lung. In addition, infection with M. avium-intracellulare occurs more frequently in cases of AIDS.

Clinical Features and Diagnosis of Tuberculosis

The clinical manifestations in tuberculosis may be variable depending upon the location, extent and type of lesions. However, in secondary pulmonary tuberculosis which is the common type, the usual clinical features are as under:

1. Referable to lungs—such as productive cough, may be with haemoptysis, pleural effusion, dyspnoea, orthopnoea etc. Chest X-ray may show typical apical changes like pleural effusion, nodularity, and miliary or diffuse infiltrates in the lung parenchyma.

2. Systemic features—such as fever, night sweats, fatigue, loss of weight and appetite. Long-standing and untreated cases of tuberculosis may develop systemic secondary amyloidosis.

The diagnosis is made by the following tests:

i) Positive Mantoux skin test
ii) Positive sputum for AFB (on smear or culture)
iii) Complete haemogram (lymphocytosis and raised ERR)
iv) Chest X-ray (characteristic hilar nodules and other parenchymal changes)
v) Fine needle aspiration cytology of an enlarged peripheral lymph node is quite helpful for confirmation of diagnosis. Causes of death in pulmonary tuberculosis are usually pulmonary insufficiency, pulmonary haemorrhage, sepsis due to disseminated miliary tuberculosis, cor pulmonale or secondary amyloidosis.

Acute Pyelonephritis

Acute pyelonephritis is an acute suppurative inflammation of the kidney caused by pyogenic bacteria.

ETIOPATHOGENESIS.

Most cases of acute pyelonephritis follow infection of the lower urinary tract. The most common pathogenic organism in urinary tract infection (UTI) is Escherichia coli (in 90% of cases), followed in decreasing frequency, by Enterobacter, Klebsiella, Pseudomonas and Proteus. The bacteria gain entry into the urinary tract, and thence into the kidney by one of the two routes: ascending infection and haematogenous infection.

1. Ascending infection. This is the most common route of infection. The common pathogenic organisms are inhabitants of the colon and may cause faecal contamination of the urethral orifice, especially in females in reproductive age group. This has been variously attributed to shorter urethra in females liable to faecal contamination, hormonal influences facilitating bacterial adherence to the mucosa, absence of prostatic secretions which have antibacterial properties, and urethral trauma during sexual intercourse. The last named produces what is appropriately labelled as 'honeymoon pyelitis'. Ascending infection may occur in a normal individual but the susceptibility is increased in patients with diabetes mellitus, pregnancy, urinary tract obstruction or instrumentation. Bacteria multiply in the urinary bladder and produce asymptomatic bacteriuria found in many of these cases. After having caused urethritis and cystitis, the bacteria in susceptible cases ascend further up into the ureters against the flow of urine, extend into the renal pelvis and then the renal cortex. The role of vesico-ureteral reflux is not of a great significance in the pathogenesis of acute chronic pyelonephritis as it is in chronic pyelonephritis.

2. Haematogenous infection. Less often, acute pyelonephritis may result from blood-borne spread of infection. This occurs more often in patients with obstructive lesions in the urinary tract, and in debilitated or immunosuppressed patients.

CLINICAL FEATURES

Classically, acute pyelonephritis has an acute onset with chills, fever, loin pain, lumbar tenderness, dysuria and frequency of micturition. Urine will show bacteria in excess of 100,000/ml, pus cells and pus cell casts in the urinary sediment. Institution of specific antibiotics, after identification of bacteria by culture followed by sensitivity test, eradicates the infection in majority of patients.

COMPLICATIONS.

Complications of acute pyelonephritis are encountered more often in patients with diabetes mellitus or with urinary tract obstruction. Following are the three important complications of acute pyelonephritis:

1. Papillary necrosis. Papillary necrosis or necrotising papillitis develops more commonly in analgesic abuse nephropathy and in sickle cell disease but may occur as a complication of acute pyelonephritis as well. It may affect one or both kidneys.

2. Pyonephrosis. Rarely, the abscesses in the kidney in acute pyelonephritis are extensive, particularly in cases with obstruction. This results in inability of the abscesses to drain and this transforms the kidney into a multilocular sac filled with pus called as pyonephrosis or renal carbuncle.

3. Perinephric abscess. The abscesses in the kidney may extend through the capsule of the kidney into the perinephric tissue and form perinephric abscess.

Chronic Pyelonephritis

Chronic pyelonephritis is a chronic tubulointerstitial disease resulting from repeated attacks of inflammation and scarring.

ETIOPATHOGENESIS.

Depending upon the etiology and pathogenesis, two types of chronic pyelonephritis are described—reflux nephropathy and obstructive pyelonephritis:

Reflux nephropathy. Reflux of urine from the bladder into one or both the ureters during micturition is the major cause of chronic pyelonephritis. Vesicoureteric reflux is particularly common in children, especially in girls, due to congenital absence or shortening of the intravesical portion of the ureter so that ureter is not compressed during the act of micturition.

Reflux results in increase in pressure in the renal pelvis so that the urine is forced into renal tubules which is eventually followed by damage to the kidney and scar formation. Vesicoureteric reflux is more common in patients with urinary tract infection, whether symptomatic or asymptomatic, but reflux of sterile urine can also cause renal damage.

Obstructive pyelonephritis. Obstruction to the outflow of urine at different levels predisposes the kidney to infection. Recurrent episodes of such obstruction and infection result in renal damage and scarring. Rarely, recurrent attacks of acute pyelonephritis may cause renal damage and scarring.

CLINICAL FEATURES

Chronic pyelonephritis often has an insidious onset. The patients present with clinical picture of chronic renal failure or with symptoms of hypertension. Sometimes, the patients may present with features of acute recurrent pyelonephritis with fever, loin pain, lumbar tenderness, dysuria, pyouria, bacteriuria and frequency of micturition. Diagnosis is made by intravenous pyelography (IVP). Culture of the urine may give positive results. Longstanding cases of chronic pyelonephritis may develop secondary systemic amyloidosis.

Syphilis

Syphilis is a venereal (sexually-transmitted) disease caused by spirochaetes, Treponema pallidum. Other treponemal diseases are yaws, pinta and bejel. The word ‘syphilis’ is derived from the name of the mythological handsome boy, Syphilus, who was cursed by Greek god Apollo with the disease.

Causative Organism

T. pallidum is a coiled spiral filament 10 µm long that moves actively in fresh preparations. The organism cannot be stained by the usual methods and can be demonstrated in the exudates and tissues by:

1. dark ground illumination (DGI) in fresh preparation;

2. fluorescent antibody technique;

3. silver impregnation techniques; and

4. PCR as a research method. The organism has not been cultivated in any culture media but experimental infection can be produced in rabbits and chimpanzees. The organism is rapidly destroyed by cold, heat, and antiseptics.

Immunology

T. pallidum does not produce any endotoxin or exotoxin. The pathogenesis of the lesions appears to be due to host immune response. There are two types of serological tests for syphilis: treponemal and non-treponemal.

A. Treponemal serological tests: These tests measure antibody to T. pallidum antigen and are as under:

i) Fluorescent treponemal antibody-absorbed (FTA-ABS) test.

ii) Agglutinin assays e.g. microhaemagglutination assay for T. pallidum (MHA-TP), and Serodia TP-PA which is more sensitive.

iii) T. pallidum passive haemagglutination (TPHA) test.

B. Non-treponemal serological tests. These tests measure non-specific reaginic antibodies IgM and IgG immunoglobulins directed against cardiolipin-lecithin-cholesterol complex and are more commonly used. These tests are as under:

i) Reiter protein complement fixation (RPCF) test: test of choice for rapid diagnosis.

ii) Venereal Disease Research Laboratory (VDRL) test: Wassermann described a complement fixing antibody against antigen of human syphilitic tissue. This antigen is used in the Standard Test for Syphilis (STS) in Wassermann complement fixing test and Venereal Disease Research Laboratory (VDRL) test.

Mode of Transmission

Syphilitic infection can be transmitted by the following routes:

1. Sexual intercourse resulting in lesions on glans penis, vulva, vagina and cervix.

2. Intimate person-to-person contact with lesions on lips, tongue or fingers.

3. Transfusion of infected blood.

4. Materno-foetal transmission in congenital syphilis if the mother is infected.

Stages of Acquired Syphilis

Acquired syphilis is divided into 3 stages depending upon the period after which the lesions appear and the type of lesions. These are: primary, secondary and tertiary syphilis.

PRIMARY SYPHILIS

Typical lesion of primary syphilis is chancre which appears on genitals or at extra-genital sites in 2-4 weeks after exposure to infection. Initially, the lesion is a painless papule which ulcerates in the centre so that the fully-developed chancre is an indurated lesion with central ulceration accompanied by regional lymphadenitis. The chancre heals without scarring, even in the absence of treatment.

SECONDARY SYPHILIS

Inadequately treated patients of primary syphilis develop mucocutaneous lesions and painless lymphadenopathy in 2-3 months after the exposure. Mucocutaneous lesions may be in the form of the mucous patches on mouth, pharynx and vagina; and generalised skin eruptions and condyloma lata in anogenital region. Antibody tests are always positive at this stage. Secondary syphilis is highly infective stage and spirochaetes can be easily demonstrated in the mucocutaneous lesions.

TERTIARY SYPHILIS

After a latent period of appearance of secondary lesions and about 2-3 years following first exposure, tertiary lesions of syphilis appear. Lesions of tertiary syphilis are much less infective than the other two stages and spirochaetes can be demonstrated with great difficulty.

These lesions are of 2 main types

i) Syphilitic gumma. It is a solitary, localised, rubbery lesion with central necrosis, seen in organs like liver, testis, bone and brain. In liver, the gumma is associated with scarring of hepatic parenchyma (hepar lobatum).

ii) Diffuse lesions of tertiary syphilis. The lesions appear following widespread dissemination of spirochaetes in the body. The diffuse lesions are predominantly seen in cardiovascular and nervous systems which are described in detail later in the relevant chapters. Briefly, these lesions are as under:

a) Cardiovascular syphilis mainly involves thoracic aorta. The wall of aorta is weakened and dilated due to syphilitic aortitis and results in aortic aneurysm, incompetence of aortic valve and narrowing of mouths of coronary ostia.

b) Neurosyphilis may manifest as: meningovascular syphilis affecting chiefly the meninges; tabes dorsalis affecting the spinal cord; and general paresis affecting the brain.

CONGENITAL SYPHILIS. Congenital syphilis may develop in a foetus of more than 16 weeks gestation who is exposed to maternal spirochaetaemia. The major morphologic features as under:

i) Saddle-shaped nose deformity due to destruction of bridge of the nose.

ii) The characteristic ‘Hutchinson’s teeth’ which are small, widely spaced, peg-shaped permanent teeth.

III) Mucocutaneous lesions of acquired secondary syphilis.

iv) Bony lesions like epiphysitis and periostitis.

v) Interstitial keratitis with corneal opacity. vi) Diffuse fibrosis in the liver. vii)Interstitial fibrosis of lungs.

viii) If the foetus with congenital syphilis is born dead, it is premature, with macerated skin, enlarged spleen and liver, and with syphilitic epiphysitis.

Histologically, the basic morphology of lesions in syphilis is seen in all the affected organs: perivascular plasma cell rich inflammatory infiltrate and endothelial cell proliferation. Many spirochaetes can be demonstrated in involved tissues.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Since the initial recognition of AIDS in the United States in 1981, tremendous advances have taken place in the understanding of this dreaded disease as regards its epidemiology, etiology, immunology, pathogenesis, clinical features and morphologic changes in various tissues and organs of the body. But efforts at finding its definite treatment and a vaccine have not yielded success so far, and thus the prognosis remains grim. Hence the global attention is presently focussed on preventive measures.

ETIOLOGIC AGENT.

AIDS is caused by an RNA retrovirus called human immunodeficiency virus (HIV) which is a type of human T cell leukaemia-lymphoma virus (HTLV). HIV resembles other HTLVs in shape and size and both have tropism for CD4 molecules present on subpopulation of T cells which are the particular targets of attack by HIV.

However, HIV differs from HTLV in being cytolytic for T cells causing immunodeficiency (cytopathic virus) while HTLV may transform the target cells into T cell leukaemia (transforming virus) (Chapter 8). Two forms of HIV have been described, HIV1 being the etiologic agent for AIDS in the US and Central Africa, while HIV2 causes a similar disease in West Africa and parts of India.

Both HIV1 and HIV2 are zoonotic infections and their origin can be traced to a species of chimpanzees who are natural reservoir of HIV and most likely source of original infection.

HIV-I virion or virus particle is spherical in shape and 100140 nm in size.

It contains a core having core proteins, chiefly p24 and p18, two strands of genomic RNA and the enzyme, reverse transcriptase. The core is covered by a double layer of lipid membrane derived from the outer membrane of the infected host cell during budding process of virus.

The membrane is studded with 2 envelope glycoproteins, gp120 and gp41, in the positions shown.

ROUTES OF TRANSMISSION.

Transmission of HIV infection occurs by one of following three routes:

1. Sexual transmission. Sexual contact in the main mode of spread and constitutes 75% of all cases of HIV transmission. Most cases of AIDS in the industrialised world like in the US occur in homosexual or bisexual males while heterosexual promiscuity seems to be the dominant mode of HIV infection in Africa and Asia. Other sexually transmitted diseases (STDs) may act as cofactors for spread of HIV, in particular gonorrhoeal and chlamydial infection. Transmission from male-to-male and male-to-female is more potent route than that from female-to-male.

2. Transmission via blood and blood products. This mode of transmission is the next largest group (25%) and occurs in 3 groups of high-risk populations: i) Intravenous drug abusers by sharing needles, syringes etc comprise a large group in the US. ii) Haemophiliacs who have received large amounts of clotting factor concentrates from pooled blood components from multiple donors. iii) Recipients of HIV-infected blood

and blood products who have received multiple transfusions of whole blood or components like platelets and plasma.

3. Perinatal transmission. HIV infection occurs from infected mother to the newborn during pregnancy transplacentally, or in immediate post-partum period through contamination with maternal blood, infected amniotic fluid or breast milk.

4. Occupational transmission. There have been a small number of health care workers (HCW), laboratory workers and those engaged in disposal of waste of sharps who have developed HIV infection by occupational exposure to HIVinfected material. It is imperative that these workers follow CDC guidelines for universal precautions which include disinfecting and sterilizing all reusable devices and use of bleaching solution for disinfecting all blood spillage.

5. Transmission by other body fluids. Although besides blood, HIV has been isolated and identified from a number of body fluids such as saliva, tears, sweat and urine, semen, vaginal secretions, cervical secretions, breast milk, CSF, synovial, pleural, peritoneal and pericardial fluid, there is no definite evidence that HIV transmission can occur by any of these fluids; isolated cases of such infection reported are in likelihood due to concomitant contamination with HIV infected blood.

PATHOGENESIS.

The pathogenesis of HIV infection is largely related to the depletion of CD4+ T cells (helper T cells) resulting in profound immunosuppression.

1. Selective tropism for CD4 molecule receptor. gp120 envelope glycoprotein of HIV has selective tropism for cells containing CD4 molecule receptor on their surface; these cells most importantly are CD4+ T cells (T helper cells); other such cells include monocyte-macrophages, microglial cells, epithelial cells of the cervix, Langerhans cells of the skin and follicular dendritic cells. Initially, HIV on entering the body via any route described above has tropism for macrophages (M-tropic) while later it becomes either dual tropic or T-tropic only and thus affects mainly CD4+ T cells which are the main target of attack by HIV.

2. Internalisation. gp120 of the virion combines with CD4 receptor, but for fusion of virion with the host cell membrane, a chemokine coreceptor (CCR) is necessary. Once HIV has combined with CD4 receptor and CCR, gp41 glycoprotein of envelope is internalised in the CD4+ T cell membrane.

3. Uncoating and viral DNA formation. Once the virion has entered the T cell cytoplasm, reverse transcriptase of the viral RNA forms a single-stranded DNA. Using the singlestranded DNA as a template, DNA polymerase copies it to make it double-stranded DNA, while destroying the original RNA strands. Viral DNA so formed has frequent mutations making the HIV quite resistant to anti-viral therapy.

4. Viral integration. The viral DNA so formed may initially remain unintegrated in the affected cell but later viral integrase protein inserts the viral DNA into nucleus of the host T cell and integrates in the host cell DNA. At this stage, viral particle is termed as HIV provirus.

5. Viral replication. HIV provirus having become part of host cell DNA, host cell DNA transcripts for viral RNA with presence of tat gene. Multiplication of viral particles is further facilitated by release of cytokines from T helper cells (CD4+ T cells): TH 1 cells elaborating IL-2 and IFN-γ., and TH 2 cells elaborating IL-4, IL-5, IL6, IL-10. RNA viral particles thus fill the cytoplasm of host T cell from where they acquire protein

coating. Released cytokines are also responsible for spread of infection to other body sites, in particular to CNS by TNF-α.

6. Latent period and immune attack. In an inactive infected T cell, the infection may remain in latent phase for a long time, accounting for the long incubation period. Immune system does act against the virus by participation of CD4+ and CD8+ T cells, macrophages and by formation of antibodies to mount attack against the virus. However, this period is short and the virus soon overpowers the host immune system.

7. CD4+ T cell destruction. Viral particles replicated in the CD4+ T cells start forming buds from the cell wall of the host cell. As these particles detach from the infected host cell, they damage part of the cell membrane of the host cell and cause death of host CD4+ T cells by apoptosis. Other proposed mechanisms of CD4+ T cell destruction are necrosis of precursors of CD4+ cells by the virus and by formation of syncytial giant cells due to attachment of more and more of gp120 molecules to the surface of CD4+ T cells.

8. Viral dissemination. Release of viral particles from infected host cell spreads the infection to more CD4+ host cells and produces viraemia. Through circulation, virus gains entry to the lymphoid tissues (lymph nodes, spleen) where it multiplies further, and are the dominant site of virus reservoir rather than circulation.

9. Impact of HIV infection on other immune cells. HIV infects other cells of the host immune system and also affects non-infected lymphoid cells. Other cells of the immune system which get infected are circulating moncytes, macrophage in tissues and dendritic follicular cells of lymph nodes. HIV-infected monocytesmacrophages do not get destroyed but instead become a reservoir of HIV infection. Infected dendritic follicular cells of the lymph nodes causes massive enlargement of follicle centres and account for persistent generalised lymphadenopathy in AIDS. Non-infected lymphoid cells include B cells, NK cells and CD8+ T cells. B cells do not have receptors for HIV but the number of B cells slowly declines, their function of immunoglobulin synthesis is impaired due to lack of activation by depleting CD4+ T cells, but instead there may be non-specific hypergammaglobulinaemia. NK cells are also reduced due to lack of cytokines from CD4+ T cells. CD8+ cells show lymphocytosis but the cells having intact function of ADCC are reduced, possibly due to CD4+ T cell quantitative loss and qualitative dysfunction (reversal of CD4+ T cells: CD8+ T cell ratio). The net result of immunological changes in the host due to HIV infection lead to profound immunosuppression rendering the host susceptible to opportunistic infections and tumours, to which he ultimately succumbs.

10. HIV infection of nervous system. Out of non-lymphoid organ involvement, HIV infection of nervous system is the most serious and 75-90% of AIDS patients may demonstrate some form of neurological involvement at autopsy. It infects microglial cells, astrocytes and oligodendrocytes as under:

i) Infection carried to the microglia of the nervous system by HIV infected CD4+ monocyte-macrophage subpopulation or endothelial cells.

ii) Direct infection of astrocytes and oligodendrocytes.

iii) Neurons are not invaded by HIV but are affected due to attachment of gp120 and by release of cytokines by HIV infected macrophages.

PATHOLOGICAL LESIONS AND CLINICAL MANIFESTATIONS OF HIV/AIDS

1. Wasting syndrome.

2. Persistent generalised lymphadenopathy.

3. GI lesions and manifestations. Almost all patients with HIV infection develop gastrointestinal manifestations. These include: chronic watery or bloody diarrhoea, oral, oropharyngeal and oesophageal candidiasis, anorexia, nausea, vomiting, mucosal ulcers, abdominal pain. These features are due to opportunistic infections (e.g. Candida, Clostridium, Shigella, Salmonella, Giardia, Entamoeba histolytica, Cryptosporium, CMV). Advance cases may develop secondary tumours occurring in GIT (e.g. Kaposi's sarcoma, lymphoma).

4. Pulmonary lesions and manifestations. Symptoms pertaining to lungs develop in about 50-75% of cases and are a major cause of death in HIV/AIDS. These features are largely due to opportunistic infections causing pneumonia e.g. with Pneumocystis carinii, M. tuberculosis, CMV, Histoplasma, and Staphylococci. Lung abscess too may develop. Other pulmonary manifestations include adult respiratory distress syndrome and secondary tumours (e.g. Kaposi's sarcoma, lymphoma).

5. Mucocutaneous lesions and manifestations. Symptoms due to mucocutaneous involvement occur in about 50 to 75% cases. Mucocutaneous viral exanthem in the form of erythematous rash is seen at the onset of primary infection itself. Other mucocutaneous manifestations are allergic (e.g. drug reaction, seborrhoeic dermatitis), infectious (viral infections such as herpes, varicella zoster, EB virus, HPV; bacterial infections such as M. avium, Staph. aureus; fungal infections such as Candida, Cryptococcus, Histoplasma) and neoplastic (e.g. Kaposi's sarcoma, squamous cell carcinoma, basal cell carcinoma, cutaneous lymphoma).

6. Haematologic lesions and manifestations. Involvement of haematopoietic system is common during the course of HIV/AIDS. These include: anaemia, leucopenia, and

thrombocytopenia. These changes are due to bone marrow suppression from several mechanisms: infections such as by HIV, mycobacteria, fungi, and parvoviruses, or by lymphomatous involvement.

7. CNS lesions and manifestations. Neurological manifestations occur in almost all cases during the course of disease and are an important cause of mortality and morbidity. These may be inflammatory, demyelinating and degenerative conditions. HIV encephalopathy or AIDSassociated dementia complex, is an AIDS defining condition and manifests clinically with deteriorating cognitive symptoms. Other pathological lesions in HIV/AIDS are meningitis (tuberculous, cryptococcal) demyelinating lesions of the spinal cord, and peripheral neuropathy and lymphoma of the brain.

8. Gynaecologic lesions and manifestations. Gynaecologic symptoms are due to monilial (candidal) vaginitis, cervical dysplasia, carcinoma cervix, and pelvic inflammatory disease.

9. Renal lesions and manifestations. Features of renal impairment may appear due to HIV-associated nephropathy and genitourinary tract infections including pyelonephritis.

10. Hepatobiliary lesions and manifestations. Manifestations of hepatobiliary tract are due to development of coinfection with hepatitis B or C, due to occurrence of other infections and due to drug-induced hepatic injury. The lesions include steatosis, granulomatous hepatitis and opportunistic infections (M. tuberculosis, Mycobacterium avium intracellulare, Histoplasma).

11. Cardiovascular lesions and manifestations. Heart disease is common autopsy finding and include a form of dilated cardiomyopathy called HIV-associated cardio myopathy, pericardial effusion in advanced disease as a reaction to opportunistic infection, lymphoma and Kaposi's sarcoma.

12. Ophthalmic lesions. HIV associated ocular manifestations occur from opportunistic infections (e.g. CMV retinitis), HIV retinopathy, and secondary tumours.

13. Musculoskeletal lesions. These include osteoporosis, osteopaenia, septic arthritis, osteomyelitis and polymyositis. 14. Endocrine lesions. Several metabolic derangements may occur during the course of disease. There is syndrome of lipodystrophy (buffalo hump) due to dyslipidaemia, hyperinsulinaemia and hyperglycaemia. There may be abnormality of thyroid function, hypogonadism and inappropriate release of ADH.

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