Chapter: 5

Pathogenesis

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Learning Objectives: At the end of the session trainees will be able to

✔ Discuss the effect of immunological response of host on presentation of the disease
✔ Describe clinical manifestation of the disease

Teaching method – Lecture discussion using power-point Presentation
5.1 Introduction: M. Lepra

Leprosy is caused by acid fast bacilli called Mycobacterium leprae (M. leprae), It is an obligate intracellular bacterium.

- It mainly affects nerves and skin. (only bacilli that can enter the nerve schwann cell)
- Bacilli have affinity for the cooler tissues.
- Bacterium invades either dermal (cutaneous) nerves or main peripheral nerve trunks situated superficially, in regions that are relatively cooler (face & limbs).

5.2 Pathogenesis of leprosy

5.2.1 Pathogenesis of leprosy

Onset of leprosy is insidious. It affects nerves, skin and eyes. It may also affect mucosa (mouth, nose, pharynx), testes, kidney, voluntary/smooth muscles, reticulo-endothelial system, and vascular endothelium.

Bacilli enter the body usually through respiratory system. It has low pathogenicity, only a small proportion of infected people develop signs of the disease. Though infected, majority of the population do not develop the disease. After entering the body, bacilli migrate towards the neural tissue and enter the Schwann cells. Bacteria can also be found in, macrophages, muscle cells and endothelial cells of blood vessels.

After entering the Schwann cells /macrophage; fate of the bacterium depends on the resistance of the infected individual towards the infecting organism. Bacilli start multiplying slowly (about 12-14 days for one bacterium to divide into two) within the cells, get liberated from the destroyed cells and enter other unaffected cells. Till this stage person remains free from signs and symptoms of leprosy.

As the bacilli multiply, bacterial load increases in the body and infection is recognized by the immunological system. Lymphocytes and histiocytes (macrophages) invade the infected tissue. At this stage clinical manifestation may appear as involvement of nerves with impairment of sensation &/ or skin patch. If it is not diagnosed and treated in the early stages, further progress of the diseases is determined by the strength of the patient’s immune response

Specific and effective cell mediated immunity (CMI) provides protection to a person against leprosy. When specific CMI is effective in eliminating/ controlling the infection in the body, lesions heal spontaneously or it produces pauci-bacillary (PB) type of leprosy. If CMI is deficient; the disease spreads uncontrolled and produces multi bacillary (MB) leprosy with multiple system involvement. Some times, the immune response is abruptly altered, either following treatment (MDT) or due to improvement of immunological status, which results in
the inflammation of skin or and nerves and even others tissue, called as leprosy reaction (types 1 and 2)

**Pathogenesis:**

![Diagram showing the pathogenesis of leprosy]

- **M. Lepae**
  - Enter through respiratory tract
  - Schwann cells in cooler places (Cutaneous nerves & peripheral nerve trunks of limbs and face)
    - Bacilli multiply in the Schwann cells

**Good CMI Response**
1. No skin/nerve lesion appear, or
2. Skin/nerve lesions appear followed by spontaneous healing, or
3. Pauci-bacillary (PB) Leprosy

**Weak CMI Response**
1. Multi bacillary / (MB) Leprosy
2. In addition to skin and nerve, eyes, testes, kidney, voluntary/smooth muscles, reticulo endothelial system, and vascular endothelium get involved

**Disabilities and deformities**

5.2.2 In **Persons with strong Cell Medicated Immunity**, granuloma formation occurs in **cutaneous nerve**. Cutaneous nerve swell and gets destroyed. Often only a few fascicles of the nerve are infiltrated but inflammation within the epineurium causes compression and destruction of unmyelinated sensory and autonomic fibers. Myelinated motor fibers are the last to get affected producing motor impairment. Severe inflammation may result in caseous necrosis within the nerve. Clinical manifestation of sensory loss occurs when, nearly 30% of the sensory fibers are destroyed.

Good CMI successfully limits the disease to the nerve Schwann cell resulting in occurrence of **pure neural leprosy**. M. leprae may escape from nerve to adjacent skin at any time and cause **classical skin lesion(s)**. Regions of the skin with relatively higher temperature such as axilla, groin, perineum and hairy scalp are usually spared.

In **persons with depressed Cell Medicated Immunity**, bacilli entering the Schwann cells multiply unchecked and destroy the nerve. Also, bacilli liberated by infected and
destroyed cells are engulfed by histiocytes. Histiocytes with bacilli inside them become wandering macrophages. Bacilli multiply inside these macrophages and travel to other tissues, through blood, lymph or tissue fluid.

5.3 Clinical Presentation of the disease

Based on the two extreme type of immune response, two polar forms (tuberculoid at one end & lepromatous at the other) of clinical presentation of the disease occur. Disease can present with clinical features representing severity, any where in the continuous /variable spectrum between these two polar forms (see Annexure No IV for an overview of Ridley and Jopling’s Immunological classification of leprosy, in the form of a continuous spectrum and Annexure III for differential diagnosis of leprosy). Person with “good” CMI response develops milder & localized form of the disease (Tuberculoid) with less bacterial load. Whereas, in persons with weak or absent CMI, develop disseminated wide spread disease (lepromatous) with high bacterial load.

5.3.1 Paucibacillary leprosy is found in people with good CMI. The disease remains localized producing a single or few skin lesions with or without peripheral nerves involvement. Skin lesions may be macule (flat)/ papule (slightly raised) and plaque. People with strong immune response are able to destroy large number of organisms and routine skin smears are usually negative in most of them.

5.3.2 Multibacillary leprosy is found in people with poor CMI. Bacilli multiply and spread more widely resulting in a generalized disease. It usually presents with widespread lesions in the skin, nerve, and to lesser extent in other organs like eyes, respiratory mucosa, testes and reticulo-endothelial system. It usually spares the central nervous system and upper reproductive system in females.

Skin lesions may be multiple (border line) or innumerable (lepromatous). In the lepromatous form lesions may be bilaterally symmetrical and ill defined macules or diffuse infiltration that may progress to formation of plaque & nodules. In addition, there may be nasal bleeding & oedema of both feet.

In the absence of treatment, paucibacillary form of leprosy may downgrade to multibacillary (from tuberculoid to lepromatous) through borderline spectrum.

5.4 Skin Lesions

Skin lesion may be the only presenting feature of the disease and can appear anywhere on the body. These lesions may be present as macule, papule, plaque, infiltration and nodule. One or more forms of lesions may be present in the same person. Skin lesions towards tuberculoid spectrum are well defined and may have complete loss of sensation where as skin lesions in borderline spectrum have impaired sensations and in those towards lepromatous spectrum (Refer Annex IV) are ill defined and do not have any loss of sensation. Temperature is the first sensation that is lost followed by light touch, pain and finally deep pressure.
5.4.1 Macule/ Patch/ Papules/ Plaques/ Nodules

Disease may start with one or more, small or large characteristic hypo-pigmented (patch lighter in colour compared to surrounding skin) or erythematous macule (Flat skin lesions), with or without hyperesthesia/ hypoesthesia/ anaesthesia.

Skin lesion may be pale, copper coloured in dark skinned people, or reddish/ erythematous in fair skinned people, but never de-pigmented (without pigment), black or dark red in colour. Indistinct lesions become more distinct on exposure to sunlight or after exercise or hot bath.

Margins of the lesion may be well defined / partially defined / ill-defined.

The whole patch may be uniformly thickened or there may be thicker outer zone with depressed / or less thickened central zone (central flattening).

Patches have reduced sensation / loss of sensation for heat, touch & pain.

Impairment/ loss of sensation is most marked in the patches on the extremities and least marked on face, more marked in the centre of the lesion than at margins.

Surface of the skin lesion may be dry, wrinkled and granular to shiny, soft and succulent.

Loss of sweating (anhidrosis) due to trophic and vasomotor disturbances in the affected area may occur quite early in the disease. Icthyosis (Dryness of skin) and chronic oedema of legs (more pronounced by evening) is usually found in lepromatous leprosy.

Hairs on the affected skin may be sparse

The nerve in the vicinity of the skin lesion (especially those entering the lesion) may be found palpably thickened with or without tenderness.

Except during the recovery phase of lepra reaction, skin lesions in leprosy are not scaly/ flaking.

Leprosy skin lesions are never congenital, seasonal.
Without treatment, the skin lesions may increase in number and size. These lesions may merge with the normal looking skin producing diffuse infiltration which may later progress to development of innumerable, wide spread bilateral papules (raised skin lesions related to surrounding skin), plaques and nodules.

Nodules are either skin colored/ erythematous/ coppery or smooth shiny without loss of sensation. Nodules are firm on palpation. It may appear in the healthy skin or on top of the existing skin lesion. Nodules are most commonly seen on face, ears. It may appear on other parts of the body or on mucous membrane of nose, pharynx & larynx. These lesions are usually seen in MB patient at the lepromatous end of the spectrum (Refer Annex IV).

Diffuse infiltrative lesion of skin may appear as shiny, thickened and slightly reddish in colour. These lesions do not show loss of sensation. In such conditions diagnosis must be confirmed by skin smear test.

**Leonine facies:** Lion like appearance of the face called leontiasis or leonine facies include the following features:

- Infiltrative skin lesions appear on cheeks, earlobes, frontal and maxillary eminences.
- Skin of the face becomes thickened due to infiltration and nodulation.
- Nose becomes swollen and broadened.
- Eye brows become thin or get completely lost.
- Normal wrinkles on the forehead and cheeks deepen and earlobes become large and hanging.

**Histoid Leproma:** A variant of MB leprosy when few to multiple firm, erythematous, round or oval, shiny glistening, well defined or pedunculated nodules may appear on the normal skin, particularly in defaulters or partially treated patients.

**5.4.2 Mucous membrane:** Mucous membrane of upper respiratory tract from nose to larynx may get infiltrated, oedematous, thickened and may even ulcerate.
Nasal Mucosa: Respiratory system is the most probable route of entrance for M. leprae. Organism infiltrates the nasal mucosa resulting in

- **Nasal congestion** due to chronic inflammation presenting as **nasal stuffiness, crust formation** inside the nasal apertures & **blood stained discharge** from nose.
- **Anosmia** (inability to smell) may be present but LAP rarely complaints of it.
- **Perforation of nasal septum:** Nodules and ulcers may appear and progress to perforation of nasal septum
- **Saddle nose deformity** due to destruction of nasal cartilage.

**Papules** may appear on **lips, tongue, palate and larynx** leading to ulceration.

- Tongue may show mild glossitis or may become deeply fissured.
- Root of tongue and peritonsillar tissue may also get involved

Exclude leprosy if, skin lesion is:

- Present since birth
- De-pigmented / has de-pigmented hairs
- Itching is present
- Removable scaly/flakes present except in resolving reversal reaction
- Show any seasonal variation

5.5 Involvement of nerves

Nerve involvement is much more serious and causes permanent and progressive disability and crippling deformities because neurons if destroyed do not regenerate and are replaced by fibrous tissue.

**Sensory deficit in a skin lesion is diagnostic of leprosy**

Consider involvement of nerve, if any of the following is present

- Thickening of nerve trunk
- Pain and tenderness in the course of the nerve
- Swelling (Abscess) in the course of the nerve
- Impairment of nerve function
Clinical manifestation of nerves involvement can occur at any stage of the disease even after completion of the treatment with MDT.

Success of management of leprosy lies in preserving the function of the nerves i.e.

- Preventing new nerve damage (if nerves are normal at the time of diagnosis)
- Prevent further deterioration of already affected nerves

5.5.1 Stages of involvement of nerves:

There are three stages of involvement of nerve

Stage I: Nerves become swollen due to inflammatory response (lepra reaction/ body’s response for invading organism) and granuloma formation. Often only a few fascicles are infected and inflammation in the epineurium sheath causes compression of the nerve within the sheath. Nerve appears palpably thickened. Pain and tingling may be felt along the course of the nerve due to ischemia caused by compression. Nerve may become tender (painful on touch) along its course without any classical evidence of impairment. If CMI can limit the infection to the nerves, with out evidence of skin involvement, disease presents as pure neural leprosy.

Stage II: Stage of nerve damage (Partial damage)

Compression of nerve trunk leads to destruction of axons due to ischemia affecting the sensory, autonomic and motor functions. Localized area of necrosis and caseation of the nerve may present as round and oval swelling in the course of the nerve indicating position of the nerve abscess. Paralysis is either partial or complete but of recent origin i.e. not more than 6-9 month old.

Nerve paralysis is incomplete if:

- Sensations are still felt in some areas of skin supplied by the affected nerve
- Loss of sensibility is partial, affecting only certain types of sensations (dissociated anesthesia)
- Some of the muscles supplied by the affected nerve are not completely paralyzed.

Stage III: Stage of nerve destruction

In long standing cases of nerve involvement (usually more than one year), nerve may become fibrosed, thin and atrophic.
Involved nerve is completely destroyed and its function cannot be recovered to any useful degree.

To summarize:

![Diagram of nerve involvement stages]

5.5.2 Essential facts about nerve involvement in leprosy.

- Nerves get involved either due to invasion by M. leprae or as part of lepra reaction and presents with pain and tenderness of the nerve. (Pressure on nerve produces pain which radiates towards the peripheral distribution of the nerve)
- Nerves superficial at some part of their course are more commonly affected in leprosy.
- Affected nerve may becomes palpably thickened in its superficial course with or without pain and tenderness (if unilateral, always compare with other side)
- Presence of unusual sensation in hands and feet like tingling, numbness, burning or feeling of heaviness may be the presenting symptoms of nerve involvement during early stage.
- Acute inflammation of the affected nerve/ compression of thickened nerve during the course of the disease may give rise to severe neuralgic pain.
- Sometimes, involvement of nerve results in loss of sensation and weakness of muscles without any preceding pain /tenderness – silent Neuropathy.
- Involvement of nerve can occur in the absence of skin lesions and is known as pure neuritic leprosy.
- Most of the nerves affected in leprosy are mixed nerves and damage to the nerve affects; sensory, autonomic and motor function of the nerve in that sequence.
- Sensory loss is more marked compared to motor dysfunction.
When a person complains of sensory disturbance such as paraesthesia or anaesthesia, a diligent search must be made for palpably thickened nerves responsible for sensory supply to that area (for sensory distribution See Section on individual nerve)

**Motor Impairment:** Stimulus to contract muscle travels from brain to muscle and this moves the body part. Neural impairment of motor function results in weakness/ paralysis (lower motor neuron type of paralysis) of the muscles supplied by the affected nerve. Normally, muscles acting around a joint keep that joint in balance. Paralysis of group of muscles around the joint produces imbalance in the muscle power around it and forces the joint to take a new position which is clinically seen as deformity. (Refer frequently seen deformities in leprosy in POD)

**Autonomic function:** Impulse from brain travels to sweat glands stimulating glands to function. Involvement of autonomic nerves may present as slight edema of hands and feet due to vasomotor disturbances. Appearance of bilateral edema of legs and ankle by end of the day may be noticed. In early stages, edema may disappear after rest at night but it may become woody with passage of time. Trophic changes in the form of loss of sweating, absence of hair and dry shiny skin are noticed in the affected area. Dryness of the skin makes it less supple and skin may crack on repeated movement of the joint.

Insensitive skin of affected hands and feet does not register pain, burns, cuts or other wounds/injuries and hence, are often neglected. The affected area may not tolerate the usual heat due to absence of reflex dilatation of the blood vessels and may develop blisters on contact with relatively hot substances.

Possibility of recovery of nerve function is high even up to 6-9 months after the complete paralysis of nerve but decreases drastically thereafter especially if duration of complete nerve paralysis is one year or more. Hence, people with complete paralysis of 6 month duration or more must be referred.

### 5.5.3 Commonly affected peripheral nerves

Nerves of face (eyes), hands and feet are commonly affected.

- Trigeminal Nerve – Corneal and Conjunctival sensation
- Ulnar nerve (upper limb) – Adduction of little finger, Clawing of little and ring finger.
- Lateral popliteal (lower limb) nerve – Foot drop
- Posterior tibial nerve. (lower limb) – Clawing of toes

**Other peripheral nerves that may be affected are:**

- Median nerve (upper limb) – Clawing of thumb, ring finger and middle finger
- Radial nerve (upper limb) – Drop wrist
- Facial nerve (face) – Inability to close eyelid completely
- Greater auricular nerve (neck) – Sensory loss at angle of lower jaw
5.6 Reactions in leprosy (Lepra Reaction)

It occurs due to sudden alteration in the immunological status of the host against the living or dead bacilli. Some times it may be the presenting feature of the disease. Reaction can occur at any time, either during the natural course of the disease, during treatment or even after the completion of treatment with MDT. Two types of acute reaction occur. These are type 1 reaction (Reversal Reaction) and type 2 reactions (Erythema Nodosum Leprosum).

Most of the deformity and disability in leprosy results from these leprosy reactions. However, leprosy reaction does not indicate the failure of treatment; rather it indicates killing of bacteria and clearance of antigen.

5.6.1 Type 1 reaction

It is a delayed hypersensitivity response (Type IV, Coombs & Gel, hypersensitivity reaction). It can occur in any clinical type of leprosy, particularly the borderline group with characteristic immunological instability. It is associated with rapid increase in specific CMI activity against the leprosy bacilli or their remnants, in patients under treatment (usually during the first six months of treatment). It is also known as Reversal Reaction.

Type 1 reaction presents as inflammation of the existing skin lesions (increase in redness, swelling, tenderness/discomfort and rarely ulceration), appearance of few new inflamed skin lesions and/or neuritis (swelling and pain of nerve). Pain in the nerve occurs due to increased intraneural pressure resulting from oedema and increased cellular infiltration. In addition, patient may present with edema of the hands and feet and sensory/motor impairment. This type of reaction is usually not associated with constitutional symptoms.

5.6.2 Type 2 reactions (Erythema Nodosum Leprosum- ENL)

Type 2 reaction is also called Erythema Nodosum Leprosum (ENL). It usually occurs in MB leprosy towards the lepromatous end of the spectrum. During the course of treatment a large number of leprosy bacilli are killed and antigen is released. These antigens combine with the existing antibodies in the tissues and blood, producing antibody antigen complexes (immune complexes) that activate the complement system, resulting in an Arthur reaction (Coombs and Gel type III). Immune complexes get deposited in various tissues with resultant inflammation. Vital organs that may get involved are eyes, testes, kidney, liver, nerve, endocardium and joints.

ENL manifests as crops of evanescent (lasting for few days) erythematous, tender, cutaneous/sub-cutaneous nodules or plaques. They are usually accompanied by constitutional symptoms like fever, malaise, anorexia and joint pain. Neuritis is often an accompanying feature.
5.7 Disabilities and deformities

Physical disability and deformity in leprosy occurs due to nerve damage (resultant sensory, autonomic and motor impairment). Autonomic impairment results in dry skin that, with added sensory impairment, results in development of callosities, blisters and trophic ulcers with day to day friction, and injury. If ulcer is neglected, it may further worsen the disability. This is compounded by muscle paralysis leading to deformities as a result of imbalance of forces across joints. Disruption of joint function exposes distal limbs to abnormal pressures which, when accompanied by sensory neglect predisposes to damage and necrosis.

Similarly, recurrent or severe inflammation of ocular tissue can cause visual impairment and even blindness.

5.8 Involvement of other tissue

As the disease progresses in untreated patients, other organs (except the central nervous system) may get affected.

**Hoarse cough & husky voice:** Involvement of laryngeal mucosa become thickened, nodulated and ulcerated and eventually progresses to fibrosis of the vocal cords resulting in immobile cords.

**Nails of fingers and toes:** Nails appear dry, lusterless, shrunken, narrowed with longitudinal ridges. However, nails are preserved, although digits become shorter and narrower due to bone atrophy & absorption.

**Bones, joints & muscles:**
- Bone changes occur in untreated disease and when started cannot be arrested even on treatment. Changes of bones in leprosy are usually confined to skull and limbs.
- In limbs deposition of bacilli in the medullary cavities, periosteum, nutrient vessels give rise to bone cysts, enlarged nutrient foramina, aseptic necrosis and spindle shaped dactylitis, periostitis of tibia, fibula and ulna.
- Neurotrophic atrophy affecting the hand is localized to phalanges. Metacarpal and carpal bones are spared whereas in feet metatarsals, tarsals and phalanges are affected. It commences in the proximal phalanges or head of the metatarsals. In the proximal phalanges, diaphysis of the bone become thin gradually by rarefying osteitis (known as concentric bone atrophy) leaving only the fine needle of the bone that disappears late. The shortened toes remain connected to the foot by soft tissue only. In the metatarsals absorption begins at the distal end of the metatarsal and it becomes thinned and pointed known as sucked candy stick appearance. Disuse osteoporosis may also be seen in the limbs with paralysis of muscles.
- Insensitive limbs are predisposed to repeated big and small injuries that result in bone atrophy and absorption. It can also lead to charcot joints in fingers, toes, wrist and ankles. Ulcers may get infected secondarily.
• **Muscle paralysis** leads to **disuse atrophy** of the muscles and in neglected cases to **fibrosis or bony ankylosis** of inter-phalangeal joints, metacarpo-phalangeal and metatarso-phalangeal joints.

**Testes:** Varying degree of testicular atrophy is likely to occur particularly if the disease is untreated or the treated patient undergoes repeated attacks of acute epididymo-orchitis during type 2 reaction. In earlier stages of testicular atrophy the patient remains sexually potent but his semen shall be devoid of spermatozoa, therefore he is sterile. Impotence and gynaecomastia of hormonal origin develops late.

**Skull:** Atrophy of the anterior nasal spine **usually occurs** due to leprous endarteritis and pyogenic osteomyelitis (due to gross ulceration of nose) and may lead to destruction of nasal cartilage and **atrophy of** maxillary alveolar process leading to **nasal collapse** (saddle deformity of the nose) and **loosening of upper central incisors or all the four incisors**.

**Reticulo-endothelial system:** There may be generalized, painless, discrete enlargement of the lymph glands in MB patients. The enlarged glands have consistency of soft rubber and changes are more marked in superficial lymph nodes esp. femoral, inguinal and epitrochlear lymph nodes. However, in type 2 reaction it may be associated with swelling and tenderness.

**Abdominal organ:** Abdominal organs especially **spleen and liver** may get infiltrated by M. leprae laden macrophages and become enlarged.

**Kidney:** **Glomerulonephritis, interstitial nephritis** and **pyelonephritis** may occur especially in severe cases. Renal amyloidosis is prevalent in some geographical areas.

### 5.9 Leprosy and pregnancy

During pregnancy sub-clinical disease may become overt and established disease may worsen due to depression of Cell mediated immunity (CMI). Increased incidence of lepra reaction occurs especially during first six months of puerperium/ lactation due to regaining of CMI. Deterioration of nerve function may occur during pregnancy and lactation. New born of leprosy affected mothers weigh less than that of healthy mothers and is at high risk of getting infected with leprosy.

### 5.10 Leprosy and HIV

There is no positive correlation between HIV positivity and development of leprosy. HIV positive patients who are put on Highly Active Anti Retroviral Therapy (HAART) may manifest leprosy (which was earlier sub-clinical) as well as Lepra Reaction. The leprosy patients with concurrent HIV may have higher incidence and severity of Lepra reactions requiring higher doses of steroids.