Leprosy: An Overview

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SUMMARY

Leprosy is a chronic infectious disease caused by Mycobacterium leprae, an acid-fast, rod-shaped bacillus. The disease mainly affects the skin, peripheral nerves, mucosa of the upper respiratory tract, eyes and also some other structures. M. leprae multiplies very slowly and the average incubation period of the disease is about 5 years. Symptoms can take as long as 20 years to appear. It is transmitted by droplet from nose and mouth, during close and frequent contact with untreated cases. Untreated, leprosy can cause progressive and permanent damage to skin, nerves, limbs and eyes. Leprosy is curable and disability can be prevented if treatment could be started earlier. Multidrug therapy (MDT) has been made available by WHO free of charge to all patients worldwide since 1995. It provides a simple yet highly effective cure for all types of leprosy.

INTRODUCTION

Leprosy is caused by Mycobacterium leprae; the Norwegian, Dr. Amauer Hansen, isolated the bacterium in 1873. It is also called the Hansen's disease after him. Leprosy is the oldest disease known to man. The earliest written records describing true leprosy came from India around the period 600BC[1]. M.leprae is only bacterium causing disease in man that has not been cultured in the laboratory[2]. Most individuals who have been contact with persons suffering from multibacillary leprosy develop a subclinical infection[3]. However, in more than 95% of such persons, the infection fails to establish itself and they never develop any manifestation of disease[3]. In 2009, the discovery of a new cause of leprosy, Mycobacterium lepromatosis, was announced[4]. Genetically M. leprae and M. lepromatosis are very similar but M. lepromatosis causes the diffuse form of lepromatous leprosy found in Mexico and Caribbean[4]. Humans are the primary reservoir of M. leprae. Animal reservoirs of leprosy have been found in 3 species: 9-banded armadillos[5], chimpanzees and mangabey monkeys.

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EPIDEMIOLOGY

Leprosy has affected humanity for over 4000 years[6], and was well recognized in the civilizations of ancient China, Egypt and India[7]. Leprosy prevalence is less than 1 per 10 000 inhabitants in the world in 2000[7]. Leprosy is most prevalent in tropical countries. Because of fear, shame and social stigma associated with this disease, leprosy is underreported. The exact number of leprosy patient is therefore not known. Worldwide over the past 20 years, more than 14 million leprosy patients have been cured, about 4 million since 2000[7]. Over 83% of all registered leprosy cases in the world are concentrated in only five countries (India, Brazil, Nigeria, Myanmer and Indonesia) and nearly three-quarters of the world's known leprosy patients are in South-East Asia[8]. In Bangladesh leprosy prevalence is 0.51/10000 population at the end of December 2004[9]. Leprosy incidence reaches a peak at 10 to 14 years and an excess of male cases has regularly been found[10].

Fig-1: M. leprae, singly and in globi [12].

BACTERIOLOGY

Mycobacterium leprae is an obligate intracellular acid fast bacillus, multiplying mainly inside the macrophage of skin and of the nerves (Schwann cells). Leprosy bacilli are pleomorphic, straight or slightly curved, rod like, Gram-positive bacteria. They may appear ovoid, fragmented or granular. In stained SSS (slit skin smear) they are seen lying singly, in clamps or in compact masses known as globi (Fig 1). The life span of normal leprosy bacillus is about 6 months. Leprosy bacilli are extremely scanty in lesions of paucibacillary leprosy but are present in enormous numbers in the lesions of multibacillary leprosy. It has the generation time ranges from 18 to 42 days[11]. The incubation period of leprosy ranges from 2 months to 40 years[12], the average being about 5 years. The leprae bacteria can be identified by SSS from lesional areas, nose blow smears, nasal scrapings and also by biopsy and histopathological examination from lesions.

PATHOPHYSIOLOGY:

The mechanism of transmission of leprosy is prolonged close contact and transmission by nasal droplet[7], followed

by hematogenous spread to skin and nerves. Malnutrition plays a role for development of overt disease. Two exit routes of M. leprae from the human body often described are the nasal mucosa and the skin. In a recent study, Job found fairly large numbers of M. leprae in the superficial keratin layer of the skin of lepromatous leprosy patients, suggesting that organism could exit along with the sebaceous secretions[13]. The importance of nasal mucosa was recognised as early as 1898 by scaffer, particularly that of ulcerated mucosa[14]. Pedley reported that the majority of lepromatous patients showed leprosy bacilli in their nasal secretions collected through blowing of the nose[15]. Davey and Rees indicated that nasal secretions from lepromatous patients could yield as much as 10 million viable organisms per day[16]. The Centers for Disease Control and Prevention (CDC) Atlanta, Georgia, notes the following assertion about the transmission of the disease: "Although the mode of transmission of Hansen's disease remains uncertain, most investigators think that M. leprae is usually spread from person to person in respiratory droplets"[17].

PATHOLOGY:

M. leprae has a predilection to Schwann cells and skin macrophages and host response is important in determining the outcome of infection. There are three important aspects of leprosy pathogenesis: the spectrum of immune response, nerve damage and immune mediated reactions. According to Ridley – Jopling spectrum of immune response, at the tuberculoid pole, well-expressed CMI and delayed hypersensitivity control bacillary multiplication; organised epitheloid granulomas are seen in tissue biopsies (tuberculoid leprosy). In the lepromatous form, there is cellular anergy towards the M. leprae, resulting in abundant bacillary multiplication (lepromatous leprosy). Between these two poles of the spectrum, there is decrease in CMI and increase in number of bacilli in the body giving rise to borderline tuberculoid, borderline and borderline lepromatous kinds of leprosy. Both T cells and macrophages are important in the response to M. leprae antigens. Tuberculoid patients have a Th-1 type response to M. leprae producing interleukin-2 and interferon-γ (INF-γ) and positive lepromin (a soluble leprosy bacillus antigen) skin tests. The strong CMI clears antigen but with local tissue destruction. Lepromatous patients have a specific cell mediated T-cell and macrophage anergy to M. leprae antigens in vitro. They are negative on lepromin skin testing. They produce Th-2 type cytokines but these are not protective. Nerve damage occurs in all types of leprosy. In tuberculoid leprosy epitheloid granuloma are formed. In lepromatous leprosy bacilli are found in skin, subcutaneous tissue, nasal mucosa, Schwann cells of the peripheral nerves, smooth muscles, sweat gland and also in other structures. Immune mediated events are responsible for leprosy reactions.

CLASSIFICATION OF LEPROSY:

There are several different approaches for classifying leprosy.

- Patients who develop clinical disease are broadly classified into two groups: patients with few organisms in their tissues (they have 5 or few lesions) are termed as paucibacillary leprosy and patients with large number of organisms (they have more than 5 lesions) are termed as multibacillary leprosy[18].
- Ridley and Jopling developed an elaborate classification based on the correlation between bacterial growth and immunological status in 196619. The relationship between CMI and bacterial growth determines the spectrum of the disease. A five- group spectrum are defined from tuberculoid, through borderline, to lepromatous, which are designated as TT, BT, BB, BL and LL. TT and LL are the polar forms of leprosy. A patient with tuberculoid form (TT) has high resistance. There are few bacteria, lesions are localized and patient is not very infectious. In lepromatous form (LL) there is little immunological resistance. There are countless bacteria and the lesions are diffuse. Patients are infectious for their environment. In the middle of the spectrum, in borderline leprosy (BT, BB, BL) immunity is variable. Immunity is more towards tuberculoid pole and less towards lepromatous pole.
- Indeterminate leprosy: They are first type skin lesions characterized by hypopigmented spots. The lesions undergo healing spontaneously or may transform to any definite type of leprosy according to immunity.
- The pure neural leprosy (PNL): The Indian classification has an additional type, the neuritic type, which is bacteriologically negative and shows neural involvement without any skin lesions.

CLINICAL FEATURES:

Indeterminate leprosy (I): Indeterminate leprosy presents as single or multiple, asymmetrical, slightly hypopigmented or faintly erythematous and usually illdefined macules on the skin. Sensation on affected area is normal or slightly impaired, while sweating and hair growth are usually unaffected. The peripheral nerves are normal. Slit-Skin Smears for AFB are mostly negative[20]. However, careful examination of well-stained serial sections usually reveals AFB in dermal nerve fibrils infiltrated with lymphocytes[21]. The lepromin test may be either negative or positive.

Indeterminate leprosy is usually self-limiting or self-healing but may progress to other forms of leprosy.

Tuberculoid leprosy (TT):

The skin lesions of tuberculoid leprosy (fig 2) are usually single, but there may be two or three asymmetrical lesions[22]. They are seldom over 10cm in diameter. Tuberculoid lesions may be reddish or brownish or hypopigmented. Hypopigmentation is due to marked reduction in the number of melanocytes[23]. The skin lesions of tuberculoid leprosy are usually oval or round in shape and are well demarcated from the surrounding skin by a distinct edge. Sensation is markedly impaired or lost in tuberculoid lesions. Sensations of light touch and temperature are usually lost earlier than sensations of pain and pressure. Damage to the nerves may produce muscle weakness or paralysis. The affected areas are symptomless (no itching), rough, and either hairless or with sparse hairs. Affected skin is dry because sweating is markedly impaired. In a few cases scaling is present and the plaques appear psoriasiform. The related peripheral nerve is usually thickened. The locally enlarged nerves may undergo caseation or liquefaction degeneration and a cold abscess thus be formed. A few bacilli may be found in skin biopsies while routine SSS for AFB is negative. The lepromin test is usually positive.

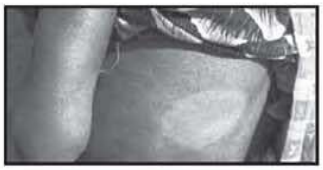

Fig 2: Well defined, hypopigmented patch in tuberculoid leprosy.

Borderline tuberculoid (BT):

There are usually few lesions and are less sharply defined and less hypopigmented than in tuberculoid leprosy. Satellite lesions around the main lesion are common. Often repeated crops of new lesions occur, thus number of lesions are more. The distribution of lesions remain asymmetrical. Hypoasthesia and impairment of hair growth are characteristic of BT leprosy. Damage to the nerves is widespread and frequently leads to crippling deformities as these patients are prone to develop type -1 lepra reaction. SSS for AFB is nil or 1+. The lepromin test is weakly positive.

Borderline leprosy (BB):

Borderline leprosy is unstable and patients have numerous skin lesions varying in size, shape and distribution. Annular lesions with a broad slightly shinning with sloping edges, dome shaped lesions or a sharply defined punched out centre are characteristic. The lesions have some tendency towards symmetrical distribution. Nerve damage is variable. SSS for AFB is 2+ to 3+. Lepromin test is usually negative or may be doubtful.

Fig-3: Numerous, copper-coloured, raised patches of borderline-lepromatous leprosy, sloping towards the periphery[12].

Boderline lepromatous (BL:Fig 3):

It is unstable and patient has numerous mostly ill defined skin lesions of macules, papules, plaques and nodules. All types of lesions may be present in single patient. Colour of the lesions is hypopigmented or erythematous with shiny surface. Sensation is usually normal or slightly impaired. The lesions have tendency to symmetrical distribution. Hair growth over the lesions is normal. Nerves are usually involved. SSS for AFB is 4+ to 5+. Lepromin test is negative.

Lepromatous leprosy (LL: fig 4):

It is generalised form of leprosy where not only skin and nerves are affected but other organs are also affected. There are diffuse infiltrations all over the body or the skin has a shiny appearance and thickened. There are numerous macules, plaques and nodules all over the body with smooth surface. The lesions may be hypopigmented or erythematous or coppery red coloured. Eye brows are usually lost and multiple nodules over the face may give rise to appearance of leonine facies. Most cases of lepromatous leprosy have developed from borderline leprosy (BB or BL), having passed through downgrading reactions 24. SSS for AFB is 5+ to 6+. Lepromin test is always negative. Rapidly multiplying leprosy bacilli may be found in lacrimal secretions, nasal mucus, discharge from ulcerating lepromatous nodules, sputum, breast milk, blood, semen and faeces. Involvement of nasal mucosa and nasal septum produce ulceration, bleeding nose and depressed nasal septum giving rise to saddle nose deformity. Eye involvement may produce painful eyes and impaired vision. Involvement of testes leads to sterility, later gynaecomastia may develop. Peripheral nerves are usually involved in later stage of disease and produce glove and stocking pattern of peripheral neuropathy. Lesions of small bones and soft tissue of hands and feet produce swollen digits, later absorption of bones and ultimately leads to mutilation (fig 5) and deformity.

Fig -4: Numerous, highly bacilliferous, shiny, glossy nodules of lepromatous leprosy[12].

Primary neuritic leprosy:

The Indian classification has an additional type, the neuritic type, which is bacteriologically negative and

Fig-5: Deformity and Mutilation of right hand [12]

shows peripheral nerve involvement without any skin lesions[25]. There is also no history of skin lesions. The male female ratio is 3:1, as against 2:1 in other types of leprosy[26]. This type of leprosy is characterized by neuritic manifestations like tingling, numbness, anaesthesia, thickening and tenderness of affected nerves, wasting of small muscles of hands and feet due to paralysis, resulting deformity.

Eye involvement in leprosy :

The eyes are frequently affected in leprosy and most eye complications occur in advanced lepromatous cases. Leprosy is a leading cause of blindness worldwide. Blindness in persons suffering from leprosy is an irreversible double tragedy, since often such persons can neither see nor feel[27]. Therefore, involvement of the eye seriously affects the patient's quality of life and causes an additional intolerable burden on him and his relatives.

Diagnostic criteria for leprosy[28]:

The diagnosis of leprosy is primarily a clinical one. In one Ethiopian study, the following criteria had a sensitivity of 97% with a positive predictive value of 98% in diagnosing leprosy. Diagnosis was based on 1 or more of 3 signs:

1. Hypopigmented or reddish patches with definite loss of sensation.
2. Thickened peripheral nerves proximal to the lesion.
3. Acid-fast bacilli on skin smears or biopsy material.

TREATMENT:

The WHO Study Group's report on the chemotherapy of leprosy in 1993 recommended two types of MDT regimen is adopted[29]. The first was a 24-month treatment for multibacillary (MB or lepromatous) cases using rifampicin, clofazimine and dapsone. The second was a 6-month treatment for paucibacillary (PB or tuberculoid) cases, using rifampicin and dapsone.

MDT remains highly effective, and patients are no longer infectious after the first monthly dose[7]. It is safe easy to use under field conditions due to its presentation in calendar blister packs[7]. Relapse rate remain low, and there is no known resistance to the combined drugs[7]. The Seventh WHO Expert Committee on Leprosy, 30 reporting in 1997, concluded that MB duration of treatment – then standing 24 months – could safely be shortened to 12 months" without significantly compromising its efficacy". The principles of treatment are outlined in Box-1.

Current WHO recommended multidrug therapy (MDT) regimen in leprosy (Box-1):

Type	Clinical features	AFB examination by SSSs	Monthly supervised treatment	Daily self administered treatment	Duration of treatment
MB cases	6 or more than 6 skin lesions or multiple nodules or thickened skin.	BI index positive or negative.	Rifampicin 600 mg Clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	12 months
	Whatever might be the number of skin rashes?	BI index positive			
PB cases	1-5 skin rashes	BI index negative	Rifampicin 600 mg	Dapsone 100 mg	6 months
	Pure neuritic/ no skin rash.	BI index negative			

COMPLICATIONS OF LEPROSY:

The most important complications of leprosy are peripreral nerve damage and lepra reactions, leading to disabilities and deformities.

REACTIONS IN LEPROSY:

The chronic course of the disease is often complicated by acute exacerbation states termed as lepra reactions. Reactions normally occur during treatment, since they are initiated by dead bacteria. Reactions may occur spontaneously or may be precipitated by intercurrent infections (viral, malaria, etc.), vaccination, anaemia, mental and/or physical stress, puberty, pregnancy, parturition or surgical interventions. They can occasionally occur before treatment or after completion of treatment. Lepra reactions are two types, Type-1 and Type-2. In patients with borderline-lepromatous leprosy, Type 1 and Type 2 lepra reactions may occur simultaneously[31].

Type-1 or "reversal" reaction or "upgrading" reaction and its management:

Type 1 or reversal lepra reaction is an example of Type IV hypersensitivity reaction (Coombs and Gell). It occurs both in PB and MB (mostly in patients with borderline leprosy-BT, BB and BL). It occurs as a result of rapid increase in CMI against leprosy bacillus or remnants of dead bacilli. Signs of inflammation are seen in existing lesions i.e. skin lesions become red, prominent, swollen and shiny and warm (Fig-6). Lesions are usually not painful but some discomfort may be felt. Sometimes, only few patches are inflamed. Nerves become enlarged, painful/tender and their sensory, autonomic and motor functions get affected. Type-1 reaction is usually not associated with systemic

features.

Fig 6: Single large patch of tuberculoid leprosy, acutely inflamed due to Type 1 lepra reaction[12].

Management: Mild reactions (no neuritis) are treated symptomatically without steroids. NSAIDs like Aspirin (adult dose 600 mg which can be given upto 6 times a day) / paracetamol (1 gm upto 4 times a day). If patient still on anti- leprosy treatment (MDT), must continue their treatment. Management of severe reactions includes:-1) admission and bed rest for 2-4 weeks in a hospital, 2) rest to the affected nerve using splint, 3) NSAIDs like aspirin is given as described above and 4) prednisolone, the main drug for treatment of severe reaction. The usual adult dose to begin with 1 mg/kg body wt. Duration of treatment is 12-24 weeks depending on severity of reaction and response to therapy. Prednisolone is gradually reduced at fortnightly interval depending on response and eventually stopped.

Type 2 reaction or Erythema Nodosum Leprosum (ENL) Reaction or downgrading type -2 reaction and its management:

Type 2 lepra reaction (erythema nodosum leprosum) is humoral hypersensitivity and it is an example of Type III hypersensitivity reaction. It occurs when large numbers of leprosy bacilli in multibacillary leprosy are killed by treatment, followed by release of their antigen. These antigens from the dead bacilli provoke an arthus type allergic reaction. Type 2 reaction can involve multiple organs and systems, causing generalized symptoms. ENL nodules (red, firm, painful tender cutaneous and subcutaneous nodules of 1-2 cm. across: fig 7) are antigen –antibody complexes that occur over nerve endings in the dermis. Immune complexes are also precipitated in the other tissues. Type -2 lepra reaction is usually associated with constitutional symptoms like high fever, joint pain, headache, bodyache, pitting edema of extremities, enlargement of lymph glands and systemic complications involving various structures like eye (iridocyclitis), ENT(epistaxis), pleurisy, pericarditis, ECG changes, myositis, glomerulonephritis, epididymo-orchitis, hepatitis, endocarditis, arthritis, tenosynovitis, painful dactylitis etc. Occasionally the ENL may become pustular and break into the skin surface. Also in the middle of the immunological range form of leprosy (i.e. in borderline leprosy- BT, BB and BL), reaction may serve to swing the patient more towards the LL end of the spectrum- "Downgrading or Type 2" Reaction. If the patient's resistance to the disease diminishes, this type of reaction is "Downgrading Type - 2", resulting in a change in the patient's immunological status with the M.leprae multiplying and spreading more throughout the body.

Management: The aim of management is to prevent nerve and organ damage. The treatment strategy includes:- 1) Increasing the dose of Clofazimine upto 300 mg day and gradually tapering of dose over 3-6 months. 2) Prednisolone, in a starting dose of 30-40 mg/day and gradually tapering over a period of 3-4 months. 3) If patient still on anti- leprosy treatment (MDT), must continue their treatment. Thalidomide is very effective and has been used to treat ENL since the 1960s[32]. One of its mechanisms of action is anti-inflammatory through selective inhibition of the pro-inflammatory cytokine TNF-alpha produced by monocytes. It is contraindicated in pregnancy. Clofazimine is less potent but extremely useful in reducing or withdrawing corticosteroids in patients who have become dependent on them. Clofazimine is the only anti-leprosy drug possessing an anti-inflammatory effect[33,34] which, if given in high doses, is clinically valuable in controlling erythema nodosum leprosum (ENL) reactions occurring in patients with multibacillary leprosy. Clofazimine-mediated, anti-inflammatory and immunosuppressive activity may be due to its stimulating effect on the synthesis of anti-inflammatory and immunosuppressive prostaglandin E2 by human polymorphonuclear leucocytes (PMNL), monocytes and macrophages in response to pro-inflammatory stimuli[35].

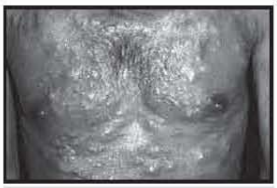

Fig 7: Erythema nodosum leprosum (ENL) lesions, pustular in places[12].

Disabilities/deformities in leprosy:

Disabilities and deformities are not inevitable in leprosy patients. Very few of the new cases will develop disabilities / deformities, when the leprosy programme detect them in the early stage of the disease, provide MDT and detect and manage complications like reaction/neuritis properly. Disability is the any restriction or lack of ability (resulting from impairment) to perform an activity considered normal for a human being. Examples: difficulty in walking due to foot-drop, slipping of a pen from the hand due to loss of sensation. Deformity is the visible alteration in the form, shape or appearance of the body due to impairment produced by the disease process. Examples: loss of eyebrows, claw hand, foot drop, clawing of toes and collapse of foot archs, lagophthalmos (pt. is unable to close the eyes) and many others.

PREVENTION AND MANAGEMENT OF DISABILITIES / DEFORMITIES:

All leprosy staffs are trained to detect early nerve involvement and employ measures in order to prevent nerve damage. The following measures are to be undertaken: a) affected peripheral nerves are identified,

b) if thickened nerve, then assessment of sensory and motor function impairment, c) if there is tender nerves or neuritis, treatment with steroid and rest of the affected part, d) education to the patient/family for about thickened nerves, neuritis.

MANAGEMENT OF DISABILITIES/ DEFORMITIES:

The main emphasis and priority for management of disabilities/deformities will be given to patient education in- a) self-care of hands, feet and eyes, b) early treatment of ulcers, injuries and wounds, c) reconstructive surgery if possible, d) and rehabilitation.

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