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Leprosy☆

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Abstract Leprosy is a granulomatous disease affecting the skin and nerves caused by *Mycobacterium leprae*. It continues to be a significant public health problem. Despite multidrug therapy, immunologic reactions continue to occur, leading to disability and deformity due to neuropathy. It is important that dermatologists are aware of the neurologic as well as the skin manifestations of the condition so that nerve involvement can be identified and treated rapidly.

Introduction

Leprosy is a chronic granulomatous infection, principally affecting the skin and peripheral nerves, caused by the obligate intracellular organism *Mycobacterium leprae*.[1]

There were 407,791 new cases diagnosed and reported to World Health Organization in 2004.[2]

It continues to be an important health problem worldwide but is most prevalent in India, Brazil, Democratic Republic of Congo, Tanzania, Nepal, Mozambique, Madagascar, Angola, and the Central African Republic.[2]

The disease causes skin lesions and neuropathy. Secondary complications of the neuropathy can result in deformity and disability. Leprosy remains a stigmatizing disease. Multidrug therapy (MDT), however, which cures the infection, has led to the understanding that leprosy can be effectively treated before disability.[3] Since 1985, 14 million individuals have received MDT.[2]

Transmission of the *M leprae* is from untreated lepromatous patients. It can persist in the environment; most people have encountered it and mount an immune response against it.

Classification

Classification of the disease is important to determine prognosis and which individuals are infectious. Classification is also important in accurately describing the epidemiology of leprosy, and the type of leprosy will dictate the treatment selected.

There are 2 systems used to classify leprosy patients. The Ridley-Jopling System[4] uses clinical and histopathological features and the bacteriological index. The different categories correlate with the activity of the host immune response (Fig. 1). It is useful because the borderline states are unstable immunologically and can be complicated by reactions. "Upgrading" reactions occur when patients develop increased cell mediated immunity, and these are associated with inflammation of skin and nerves. "Downgrading" occurs before treatment when borderline patients lose cell-mediated immunity and move toward the lepromatous pole.

A simplified classification based on the number of skin lesions is used in the field when slit-skin smears are

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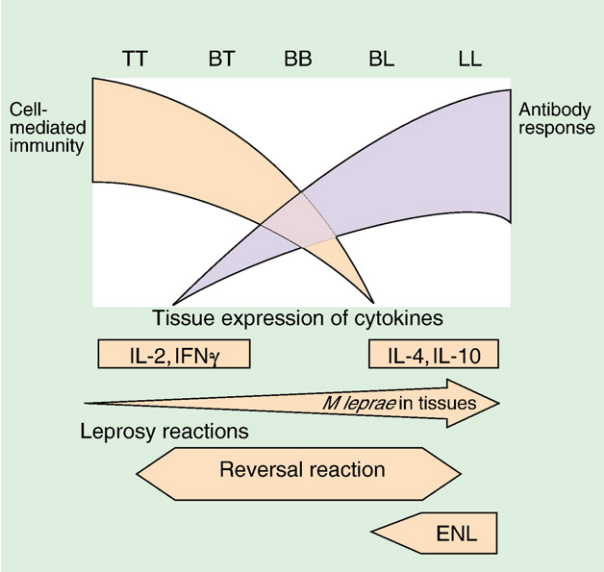

Fig. 1 The Ridley-Jopling Classification and the relationship with host immunity.

unavailable. It is a quick and useful tool, which can be used by a wide variety of health care providers (Table 1). It may, however, lead to overtreatment as more than 60% of multibacillary patients have a negative bacterial index (BI) (see later) and, so, only require 2-drug rather than 3-drug MDT.[5]

Clinical features

The clinical features of the disease are determined by the host response to *M leprae*. Patients commonly present with skin lesions, numbness or weakness caused by peripheral nerve involvement, or more rarely, a painless burn or ulcer in an anesthetic hand or foot. A leprosy reaction may be a presenting feature of the disease.[7] Nerve pain misdiagnosed as joint pain may result in a person being labeled as having arthritis.

In nonendemic areas, the diagnosis is frequently delayed because leprosy is not considered and patients may present to a wide range of specialists.[8]

Skin involvement

Early skin lesions may be rather poorly defined hypopigmented or erythematous macules. Sensation in these early stages may be unaltered. The histology of early skin lesions do not show evidence of granuloma formation. There is a nonspecific inflammatory infiltrate around skin appendages.

Table 1 World Health Organization operational classification of leprosy[6]

Leprosy type	No. of skin lesions
Paucibacillary	1-5
Multibacillary	>5

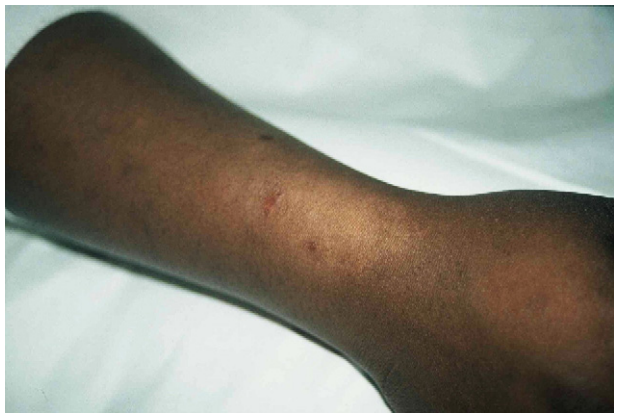

Fig. 2 Well-defined hypopigmented tuberculoid lesion.

Tuberculoid disease is characterized by a single or very few lesions. These are macules or plaques with well-defined edges (Fig. 2). The plaques are often flattened in the center. In dark skin, hypopigmentation predominates over the erythema or copper color more easily seen in lighter skin. The lesions are frequently scaly, dry, and hairless. Tuberculoid lesions histologically have granulomas surrounding neurovascular elements and extend into the papillary dermis. Acid-fast bacilli are not seen.

Lepromatous disease may be present for many years before diagnosis, and the early skin changes are widely and symmetrically distributed macules. They are poorly defined

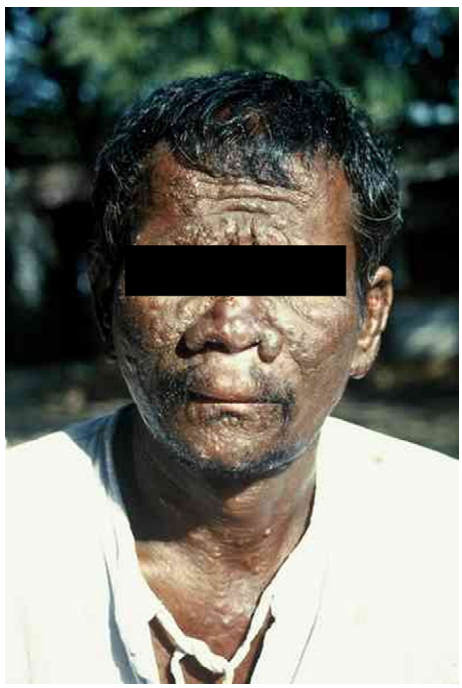

Fig. 3 The leonine facies of lepromatous disease.

with mild hypopigmentation and erythema. Flesh-colored or occasionally erythematous papules and nodules may be present. Peripheral edema of the legs and ankles due to increased stasis occurs. The skin, if left untreated, thickens because of dermal infiltration giving rise to the "leonine facies" (Fig. 3). Hair is lost from affected skin, notably from eyelashes and eyebrows (madarosis). Scalp hair is usually spared due to the higher temperature of the scalp,[9] but in leprous alopecia, hair only grows over the course of scalp arteries. Patchy alopecia has also been reported in borderline cases.[10] The ear lobes thicken. The skin of the legs becomes ichthyotic and thickened. Ulceration of involved skin may also occur.

Skin lesions in lepromatous disease have an atrophic epidermis with loss of the rete ridges histologically. The papillary dermis appears as a clear band, whereas the deeper dermis is diffusely infiltrated with macrophages, lymphocytes, and plasma cells. There are abundant acid-fast bacilli singly or in clumps.

Borderline leprosy shows skin lesions intermediate between the 2 polar forms. The morphology of lesions may be macular, papulonodular, plaquelike, annular, or with a geographic appearance. The midborderline state has characteristic plaques with well-demarcated, depressed, or "punched-out" (but not ulcerated) areas within it—sometimes referred to as a "Swiss cheese" appearance.

The formation of small granulomas is characteristic of borderline leprosy, the granulomas becoming more diffuse from borderline tuberculoid (BT) to borderline lepromatous (BL) disease.

Mycobacterium leprae have been demonstrated in hair follicles located in the dermal papilla and the outer root sheaf during anagen and telogen in untreated lepromatous patients. The formative process of the hair shafts, root sheaths, and pigmentation was not affected, but the authors postulated that changes in the biochemical environment of the dermal papilla may be responsible for hair loss.[11]

The nail changes observed in leprosy result from the peripheral neuropathy and are not specific to the disease. Trauma, vascular impairment, and infection all contribute in varying degrees.[12]

Nerve involvement

Nerve involvement in leprosy affects sensory, motor, and autonomic function of peripheral nerves. Sensory loss is the earliest and most frequently affected modality, but a predominantly motor loss can also occur. Granulomatous inflammation of peripheral nerves causes palpable enlargement, which may or may not be painful and causes sensory and motor loss in the distribution of the affected nerve. Enlarged nerves can also be damaged because of entrapment within fibroosseous tunnels. Reactions cause further nerve damage.

Leprosy most commonly affects the posterior tibial nerve causing anesthesia on the soles of the feet followed by the ulnar, median, lateral popliteal, and facial nerves.[13] Other nerves affected by the disease include the greater auricular, radial, and radial cutaneous nerves.

The presence of a skin lesion overlying a major nerve trunk is associated with a significant increase in risk of impairment in that nerve.

Small dermal nerves can be affected, leading to reduced sensation and loss of sweating in tuberculoid and borderline tuberculoid lesions and a glove and stocking sensory loss in lepromatous disease.

Involvement of autonomic fibers causes a reduction in sweating in skin patches, and a glove and stocking hypohidrosis also occurs. Direct involvement of the glands themselves also affects the ability of affected areas to sweat.[14]

Pure neuritic leprosy affects peripheral nerve trunks in the absence of cutaneous signs and may be any type of leprosy.

Silent neuropathy is an insidious deterioration in sensory or motor function without signs or symptoms of inflammation.[15]

The effect of the disease on nerves leads to disability and deformity. This occurs through impaired sensation leading to trauma and secondary infection (including osteomyelitis), which causes tissue damage. Loss of motor function produces disability, and the increased dryness of the involved skin makes it more vulnerable to damage.

It is of the utmost importance that a complete motor and sensory neurologic assessment is carried out at each clinical visit to ensure that nerve function is not deteriorating especially because this can be asymptomatic.

Eye involvement

Blindness affects 5.3% of individuals with leprosy. Leprosy is the cause of the blindness in 3.2%.[16] Blindness can have devastating consequences for those who probably already have sensory loss of the hands and feet. The disease compromises the eye through nerve damage and by direct bacillary invasion of the skin or eye itself. These factors can occur in combination and result in the 4 main causes of visual loss: lagophthalmos (an inability to close the eyes normally), corneal ulceration, acute or chronic iridocyclitis, and secondary cataract.

Lagophthalmos usually results in damage to the zygomatic and temporal branches of the facial (VIIth) nerve. It gives rise to exposure keratopathy. Reduced corneal and conjunctival sensation due to involvement of the ophthalmic branch of the trigeminal (Vth) nerve predisposes to corneal ulceration.

In lepromatous disease, madarosis results in increased amounts of irritants entering the eye, which may give rise to a sensation of itch. This leads to rubbing, which can cause

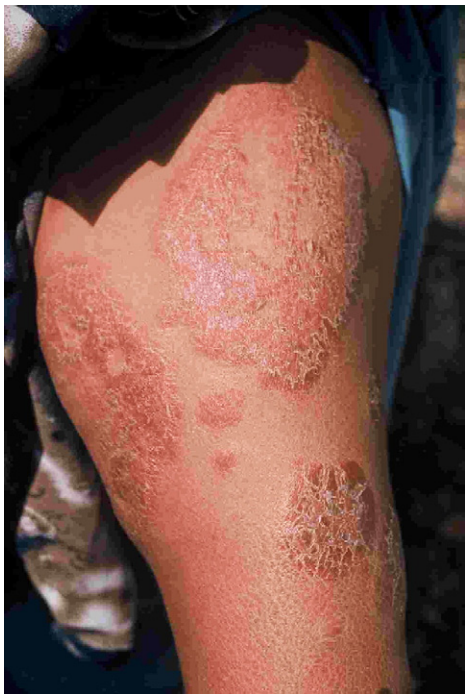

Fig. 4 Type 1 reaction.

further trauma to the eye. Involvement of the nasal mucosa can lead to recurrent infections of the lacrimal system. Infiltration of the eye itself by *M leprae* causes reduced sensation by damage to small nerve fibers and increases the risk of inflammation in the eye due to antigenic stimulation. Other sight-threatening conditions occurring concomitantly should also be considered.

Mucosal involvement

Lepromatous involvement of the nasal mucosa gives rise to the sensation of nasal stuffiness and epistaxis. Infiltration of nasal structures may lead to a saddle deformity due to septal perforation and destruction of the anterior nasal spine.

In advanced lepromatous disease, the tongue may become infiltrated, and deep fissures and ulceration occur. Laryngeal involvement, although extremely rare nowadays, was life-threatening in the days before effective chemotherapy.

Other system involvement and complications

The involvement of other systems is usually seen in lepromatous disease due to bacillary infiltration of structures and organs. Testicular atrophy results from infiltration and the acute orchitis of erythema nodosum leprosum (ENL). Men who have had ENL orchitis should be investigated to define the extent of any hypogonadism where such facilities are available. Amyloid and renal disease rarely complicate leprosy since the advent of MDT.

Type 1 (reversal) reactions

Type 1 reactions occur in borderline disease, and 30% of individuals with borderline leprosy are at risk for type 1 reaction.[17] A type 1 reaction is characterized by acute inflammation in skin lesions (Fig. 4) or nerves or both. The skin lesions become acutely inflamed and edematous and may ulcerate. Edema of the hands, feet, and face can also be a feature of a reaction, but systemic symptoms are unusual. Acute neuritis leads to nerve function impairment if not treated rapidly and adequately leads to permanent loss of nerve function, causing peripheral sensory and motor neuropathy. Type 1 reactions are frequently recurrent, and this can lead to further nerve damage.[17] Type 1 reactions can occur at any time but are frequently seen after starting MDT or during the puerperium.

Erythema nodosum leprosum reactions

Erythema nodosum leprosum is a reactional state that affects 20% of lepromatous and 10% of borderline lepromatous cases. The greater the infiltration of the skin and the higher the BI, the greater the risk of developing ENL.[18] Erythema nodosum leprosum is a systemic disorder affecting many organ systems. The onset is acute, but it may pass into a chronic phase and can be recurrent. Erythema nodosum leprosum is caused by immune complex deposition and is associated with high levels of tumor necrosis factor–α.[19]

Erythema nodosum leprosum produces fever and, in the skin, painful and tender red papules or nodules (Fig. 5), which occur in crops often affecting the face and extensor surfaces of the limbs. The lesions may be superficial or deep, causing a panniculitis. Bullous ENL has been described,[20] and lesions may ulcerate. Subcutaneous tissue involvement may lead to tethering and fixation to joints, causing loss of function. Erythema nodosum leprosum reactions may also produce uveitis, neuritis, arthritis, dactylitis (Fig. 6), lympadenitis, and orchitis. The recurrent

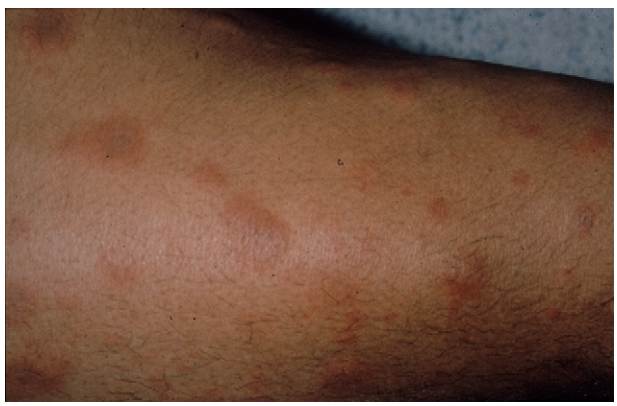

Fig. 5 Erythema nodosum leprosum.

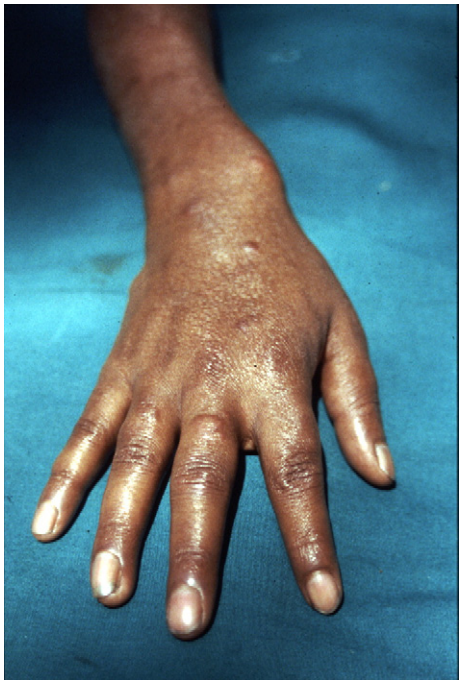

Fig. 6 Erythema nodosum leprosum with dactylitis.

inflammation of organs can lead to blindness and sterility. The hypogonadism can also result in gynecomastia.

Lucio phenomenon

This is a very rare reactional state occurring in lepromatous disease, which presents as painful irregular patches. They become purpuric, and bullae form that break down, leaving widespread areas of ulceration.[21] Healing is with scarring. Lucio reaction is associated with severe systemic upset and may be fatal. The mechanism is a cutaneous vasculitis, which is thought to be due to infiltration of the skin, causing an inflammatory microthromboembolic occlusion of the dermal vasculature.[22] Lucio phenomenon was first described in Mexico and was thought to be confined to the western hemisphere, but cases from India have been reported.

Pregnancy

A systematic literature review of the interaction between leprosy and pregnancy highlighted an association between the development of type 1 reactions and neuritis and parturition when cell-mediated immunity returns to the prepregnant level.[23]

Erythema nodosum leprosum reactions occur throughout pregnancy and lactation, and the onset of nerve damage is earlier than in those who are not pregnant. There is little evidence that pregnancy promotes infection or relapse of the disease.

Leprosy and HIV

The fear that HIV infection would increase susceptibility to *M leprae* does not appear to have been realized, nor does it alter the clinical features of leprosy. Leprosy in HIV-positive individuals does not appear to be shifted to the lepromatous pole, nor does it develop quicker. The response to MDT is also unaffected. Reactions in individuals with coinfection may occur with increased frequency, but there are conflicting data concerning the response to treatment in this group.

Latent leprosy infections may be unmasked as immune reconstitution disease after the initiation of antiretroviral therapy. The improvement in immune function restores the host ability to form granulomas. The reported cases have all been borderline cases complicated by type 1 reaction.[24]

Diagnosis

The diagnosis of leprosy remains a clinical one. The presence of skin lesions with definite sensory loss or thickened peripheral nerves or the demonstration of *M leprae* on slit-skin smears or on histology of tissue (skin or nerve) is diagnostic (Table 2).

Differential diagnosis

The manifestations of leprosy are protean, and the differential diagnosis is therefore wide. The consideration of leprosy as a diagnosis and adherence to the clinical criteria for diagnosing leprosy will facilitate a correct diagnosis. It can be difficult to diagnose leprosy especially in nonendemic regions or where the prevalence is very low.

Congenital lesions such as nevus depigmentosus have normal sensation and are present at birth. Vitiligo is depigmented rather than hypopigmented. Pityriasis alba can be difficult to distinguish from early disease. Pityriasis versicolor and dermatophyte infection may cause diagnostic difficulty. A history of preceding trauma or inflammation should be sought to rule out postinflammatory hypopigmentation. The importance of differentiating relatively benign hypopigmented skin changes from leprosy was emphasized by a recent study from Mali.[25]

In some parts of the world, leprosy is a more common cause of granulomatous lesions than sarcoid, granuloma multiforme, cutaneous tuberculosis, and granuloma annulare.

Table 2 Diagnostic features of leprosy

• Skin lesions with definite sensory loss[a]
• Thickened peripheral nerves
• Acid-fast bacilli on skin smears or tissue biopsy

[a] Skin lesions at the BL/LL end of the spectrum may not have demonstrable sensory loss.

Cutaneous leishmaniasis does not usually produce as many nodules as lepromatous leprosy, and the lesions usually crust and ulcerate after weeks or months. Post kala-azar dermal leishmaniasis may present with papules and hypopigmented macules and nodules, which may mimic lepromatous leprosy.

Nerve thickening is a feature of hereditary sensory motor neuropathy type III and Refsum's disease. Amyloid, which itself can complicate leprosy, can cause nerve thickening, and nerve enlargement due to neurofibromatosis mimicking leprosy has been reported.[26]

Investigations

The diagnosis is usually made clinically but is supported by slit-skin smears and skin biopsy.[7] *Mycobacterium leprae* cannot be cultured in vitro.

The BI is a logarithmic scale (1-6) quantifying the density of *M leprae* on a slit-skin smear and is used to assess response to treatment.

Rarely, nerve biopsy may be needed to confirm the diagnosis and should be performed on a purely sensory nerve (eg, radial cutaneous or sural nerve).

Treatment—chemotherapy

All patients should receive a multidrug combination, and the first-line agents are rifampicin, clofazimine, and dapsone. Multidrug therapy was introduced in 1982 after the emergence of resistance to dapsone-only regimens.[27] Since then, there has been debate over how long multibacillary MDT should be taken.

The World Health Organization reduced the recommended treatment period for multibacillary disease from 24 to 12 months (Table 3),[6] but this remains under review, and so many authors advocate 24 months for patients with a BI greater than 4 at diagnosis until further evidence becomes available.

Rifampicin-ofloxacin-minocycline single-dose treatment has been used for paucibacillary single lesion disease or as a monthly supervised paucibacillary regimen in certain settings. The long-term effectiveness needs to be fully evaluated.[28]

Relapse rates after MDT vary from 0% to 2.5% in paucibacillary disease. In multibacillary disease, the published rates of relapse are between 0% to 7.7%.[29] The study with the highest relapse rate in multibacillary patients demonstrated that 90% of relapses occurred in patients with a BI greater than 4.

Patients should be advised of the common side effects of these drugs to avoid unnecessary anxiety and inappropriate cessation of therapy.

Rifampicin causes an orange-red discoloration of body fluids for 48 hours after ingestion.

Clofazimine causes red-brown skin and conjunctival discoloration and darkening of involved skin, which can range from red through purple or black.[30] This unpleasant effect may make the drug unacceptable to some patients, particularly if cosmetically sensitive sites are affected. The discoloration fades slowly on withdrawal of the drug. Clofazimine also causes an ichthyosis on the shins and forearms.[30] Clofazimine crystals may be deposited in tissues that, in the bowel, can cause an enteropathy.[31]

Dapsone causes hemolysis, which may be severe especially in individuals with glucose-6-phosphate dehydrogenase deficiency[32] and is rarely associated with a hypersensitivity syndrome.[33]

In individuals unable to take clofazimine or dapsone, other agents such as minocycline, clarithromycin, ofloxacin, or pefloxacin are active against *M leprae*[4] and can all be used as second-line agents. Minocycline causes slate gray skin discoloration in some individuals.[34]

Nerve damage can occur before, during, or after MDT, and so, it is essential that monitoring for this is done during MDT. Patients with multibacillary disease, nerve impairment before MDT, or both should be followed up for 2 years.[35]

Treatment and management of reactions

Leprosy reactions should be managed by a specialist. Reactions may be a presenting feature of the disease or occur during MDT or even after it has been completed. The treatment of type 1 reactions is aimed at controlling the acute inflammation, easing pain and reversing eye and nerve damage. Multidrug therapy should be continued during a reaction. Moderately inflamed skin plaques or neuritis are treated with oral corticosteroids. Different regimens have been used, but prednisolone 40 to 60 mg daily was decreased by 5 mg every 2 to 4 weeks after demonstration of improvement. Despite prolonged oral prednisolone, only 60% will show improvement in nerve function.[36] Skin lesions readily respond.

Table 3 World Health Organization–recommended MDT regimens

Type of leprosy	Drug treatment		Length of treatment (mo)
	Monthly supervised	Daily, self-administered	
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6
Multibacillary	Rifampicin 600 mg + clofazimine 300 mg	Clofazimine 50 mg + dapsone 100 mg	12

A 4-month course of prophylactic steroids have been tried in the prevention of type 1 reactions, and they were effective early on, but at 12-month follow-up, the protective effect had been lost.[37] The management of silent neuropathy is similar to that of type 1 reactions.

Most ENL reactions require immunosuppression. The more severe ones require high doses of corticosteroids, usually starting with prednisolone 60 mg daily.[39] The recurrent nature of the condition means that steroid-induced side effects may become a significant problem. Thalidomide 300 to 400 mg daily has a dramatic effect in controlling ENL and preventing recurrences. Its use is limited due to teratogenicity (phocomelia) and possible neurotoxicity (although this does not appear to be a problem in leprosy patients). Clofazimine and pentoxifylline have been used in ENL, but they are less effective than prednisolone or thalidomide.[38,39] Colchicine and chloroquine have also been used with limited effect.

It remains to be seen whether tumor necrosis factor–α blockade with biologic agents will have a role to play in the management of ENL, but tuberculosis (TB) and cost may limit their use especially in endemic areas.

Education

It is important to carefully explain the nature of the disease to the patient and that it is curable. It should be emphasized that deformity and disability are not inevitable and that the disease is not hereditary. Multidrug therapy renders those who are infectious safe to close contacts within 72 hours, and a completely normal social life should be encouraged. It should be made clear that transmission of the disease does not occur through sexual contact. Most people diagnosed with leprosy do not have a history of contact with another affected individual.

Prevention of disability

Minimizing nerve damage by detecting deterioration in nerve function early and instituting steroid therapy quickly is essential in preventing disability.

The prevention of secondary damage to neuropathic areas is essential. It is important to make the patient aware of activities that put these areas at risk and to give advice about orthotics and protective footwear. Individuals should also be advised to undertake self-examination to identify any areas of trauma. It has been demonstrated that training people in self-care can reduce the requirement for admission to hospital with plantar ulceration.[40]

Damaged neuropathic areas should be protected from further damage by resting the area, and any secondary infection should be treated with appropriate antibiotics. Surgical intervention may be required to debride necrotic tissue and allow drainage of any collection.

Reconstructive surgery may have a role in trying to improve function if contractures occur, if there is foot drop, or when there is eye involvement.

Socioeconomic rehabilitation

General community-based projects involving family and the wider community have been shown to help best with rehabilitation.[41] The development of these has been assisted by the International Association for Integration, Dignity and Economic Advancement.

Eradication of leprosy

The eradication of leprosy has not been achieved despite more than 20 years of MDT. Lepromatous patients are highly infectious, and the organism can remain viable outside a human host for many months. The mean incubation time of lepromatous disease is 10 years. These factors make it difficult to completely eradicate the disease.

It must be remembered that dealing with leprosy is not simply a matter of treating the infection of *M leprae* with MDT. It also requires the prompt management of reactions that cause further damage, which may occur even after a course of MDT has been finished and the organism is dead. Dealing with the complications of neuropathy and minimizing the impact of the disease on physical, psychological, and social well-being is vital.

References

1. Lockwood DNJ. Leprosy. In: Burns DA, Breathnach SM, Cox NH, Griffiths CEM, editors. Rook's textbook of dermatology, vol. 2. 7th ed. Oxford: Blackwell Publishing; 2004. p. 29.1-29.21.
2. Global leprosy situation. Wkly Epidemiol Rec 2005;80:289-95.
3. Britton WJ, Lockwood DNJ. Leprosy. Lancet 2004;363:1209-19.
4. Ridley DS, Jopling WH. Classification of leprosy according to immunity. Int J Lepr 1966;34:255-73.
5. van Brakel WH, Nicholls PG, Das L, et al. The INFIR Cohort Study: investigating prediction, detection and pathogenesis of neuropathy and reactions in leprosy. Methods and baseline results of a cohort of multibacillary leprosy patients in north India. Lepr Rev 2005;76:14-34.
6. www.who.int/lep/disease/Eliminate_Leprosy_V8.pdf
7. Pfaltzgraff RE, Ramu G. Clinical leprosy. In: Hastings RC, editor. Leprosy. 2nd ed. Edinburgh: Churchill Livingstone; 1994. p. 237-90.
8. Lockwood DNJ, Reid AJC. The diagnosis of leprosy is delayed in the United Kingdom. Q J Med 2001;94:207-12.
9. Brand PW. Temperature variation and leprosy deformity. Int J Lepr 1959;27:1-7.
10. Abraham S, Ebenezer GJ, Jesudasan K. Diffuse alopecia of the scalp in borderline-lepromatous leprosy in an Indian patient. Lepr Rev 1997;68:336-40.
11. Gummer CL, Starley JN, Dawber RP, Pearson JM. The distribution of *Mycobacterium leprae* in the hair follicle of the eyebrow. Int J Lepr Other Mycobact Dis 1983;51:205-10.
12. Pakti AH, Baran R. Significance of nail changes in leprosy: a clinical review of 357 cases. Semin Dermatol 1991;10:77-81.

13. Croft RP, Richardus JH, Nicholls PG, Smith WC. Nerve function impairment in leprosy: design, methodology, and intake status of a prospective cohort study of 2664 new leprosy cases in Bangladesh (The Bangladesh Acute Nerve Damage Study). Lepr Rev 1999;70:140-59.
14. Facer P, Mathur R, Pandya SS, et al. Correlation of quantitative tests of nerve and target organ dysfunction with skin immunohistology in leprosy. Brain 1998;121:2239-47.
15. van Brakel WH, Khawas IB. Silent neuropathy in leprosy: an epidemiological description. Lepr Rev 1994;65:350-60.
16. ffytche TJ. The prevalence of disabling ocular complications of leprosy: a global study. Indian J Lepr 1998;70:49-59.
17. van Brakel WH, Khawas IB, Lucas SB. Reactions in leprosy: an epidemiological study of 386 patients in West Nepal. Lepr Rev 1994; 65:190-203.
18. Manandhar R, LeMaster JW, Roche PW. Risk factors for erythema nodosum leprosum. Int J Lepr Other Mycobact Dis 1999;67:270-8.
19. Sarno EN, Grau GE, Vieira LM, Nery JA. Serum levels of tumour necrosis factor-alpha and interleukin-1 beta during leprosy reactional states. Clin Exp Immunol 1991;84:103-8.
20. Rijal A, Agrawal S, Agarwalla A, Lakhey M. Bullous erythema nodosum leprosum: a case report from Nepal. Lepr Rev 2004;75:177-80.
21. Moschella SL. Primary diffuse lepromatous leprosy with erythema necrotisans (Lucio phenomenon). Arch Dermatol 1968;97:593-4.
22. Sehgal V. Contemplative immune mechanism of Lucio phenomenon and its global status. J Dermatol 1987;14:580-5.
23. Lockwood DNJ, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. Int J Lepr Other Mycobact Dis 1999;67:6-12.
24. Ustianowski A.P, Lawn SD, Lockwood DNJ. Interactions between HIV infection and leprosy: a paradox. Lancet Infect Dis 2006;6:350-60.
25. Faye O, N'Diaye HA, Keita S, et al. High prevalence of non-leprotic hypochromic patches among children in a rural area of Mali, West Africa. Lepr Rev 2005;76:144-6.
26. Naik RP, Srinivas CR, Rao RV. Thickening of peripheral nerves in neurofibromatosis. Indian J Lepr 1985;57:876-8.
27. World Health Organisation. Chemotherapy of leprosy for control programmes. Tech Rep Ser. Geneva: WHO; 1982. p. 675.
28. Lockwood DNJ, Kumar B. Treatment of leprosy. BMJ 2004;328: 1447-8.
29. www.clinicalevidence.com
30. Jopling WH. Complications of treatment with clofazimine (Lamprene: B663). Lepr Rev 1976;47:1-3.
31. Atkinson Jr AJ, Sheagren JN, Barba Rubio J, Knight V. Evaluation of B.663 in human leprosy. Int J Lepr Other Mycobact Dis 1967;35: 119-27.
32. Degowin RL, Eppes RB, Powell RD, Carson PE. The haemolytic effects of diaphenylsulfone (DDS) in normal subjects and in those with glucose-6-phosphate-dehydrogenase deficiency. Bull World Health Organ 1966;35:165-79.
33. Tomecki KJ, Catalano CJ, Cross H, Newcombe L. An intensive self care training programme reduces admissions for the treatment of plantar ulcers. Lepr Rev 2001;72:276-84.
34. Simons JJ, Morales A. Minocycline and generalized cutaneous pigmentation. J Am Acad Dermatol 1980;33:244-7.
35. Croft RP, Nicholls PG, Steyerberg EW, et al. A clinical prediction rule for nerve function impairment in leprosy patients-revisited after 5 years of follow-up. Lepr Rev 2003;74:35-41.
36. van Brakel WH, Khawas IB. Nerve function impairment in leprosy: a clinical and epidemiological study—Part 2. Results of steroid treatment. Lepr Rev 1996;67:104-18.
37. Smith WC, Anderson AM, Withington SG, et al. Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). BMJ 2004;328:1459.
38. WHO Expert Committee on Leprosy—Fifth Report. Tech Rep Ser. Geneva: World Health Organisation; 1977. p. 607.
39. Moreira AL, Kaplan G, Villahermosa LG, et al. Comparison of pentoxifylline, thalidomide and prednisone in the treatment of ENL. Int J Lepr Other Mycobact Dis 1998;66:61-5.
40. Cross H, Newcombe L. An intensive self care training programme reduces admissions for the treatment of plantar ulcers. Lepr Rev 2001; 72:276-84.
41. Nicholls PG. Guidelines for social and economic rehabilitation. Lepr Rev 2000;71:422-65.