Update on leprosy

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Leprosy, a result of infection by Mycobacterium leprae, is a leading cause of peripheral neuropathy. The World Health Organization aimed to eliminate leprosy as a public health problem by 2000, but this has not been attained. Patients with leprosy continue to present in the UK. The diagnosis of leprosy is frequently not considered, with resultant pathological and psychological problems for patients.

In 1873, the Norwegian Armauer Hansen discovered that leprosy was caused by *Mycobacterium leprae*. Infection with this bacterium results in a chronic infectious granulomatous disease. *M. leprae* invades the skin and nerves, causing peripheral neuropathy and skin lesions. It is one of the oldest recorded diseases. In 1988, the World Health Organization (WHO) proposed to eliminate leprosy by the year 2000. However, this has proved too ambitious, with India detecting over 600 000 new cases and Brazil a further 44 000 new cases in 1999.

Leprosy is a disease that British doctors often fail to diagnose, with unfortunate consequences for the patients. In a recent series, 40% of new UK cases had severe neuropathy at presentation (Van Buynder et al, 1999). Doctors need to recognize leprosy since it is curable, and prompt treatment can reduce nerve damage and the tremendous associated stigma.

EPIDEMIOLOGY

Leprosy remains a public health problem in 24 countries, mainly in the tropics, with a prevalence rate greater than 1 case per 10 000 population. The top six endemic countries are India, Brazil, Madagascar, Indonesia, Myanmar and Nepal, with India accounting for 67% of the prevalence and 73% of the detection worldwide (WHO, 2000).

In 1999, there were just under 1 million cases registered on treatment worldwide, which represents a reduction in prevalence by 86% since the introduction of effective treatment. However, there are still a large number of childhood cases, which suggests ongoing transmission.

Although, since 1999, the number of new cases is stable at around 700 000 per year, concern remains that incidence is not declining since detection is still not optimal in geographically remote areas and under-reporting, as a result of the stigma, still occurs.

In England and Wales, where leprosy is a notifiable disease, a total of 1358 cases have been registered since 1951 (Van Buynder et al, 1999). There are still 128 individuals who are on treatment or under surveillance. Since 1993, approximately nine new cases per year have been notified. Half of the new cases in the UK are in migrants from the Indian subcontinent, and there are a few cases in Caucasians who have lived in leprosy endemic areas for prolonged periods, i.e. between 8–42 years (Lockwood, 2000).

Leprosy has a long incubation period (2–10 years), so patients can present long after leaving endemic areas. Leprosy must be considered in those who have spent any time in leprosy endemic countries and particularly Asia.

TRANSMISSION

M. leprae is transmitted via the nasal discharge of untreated lepromatous patients and enters via the nose leading to haematogenous spread to the skin and peripheral nerves. However, contact probably has to be prolonged with those untreated patients who have a high bacterial load (Dockrell et al, 1991).

PATHOLOGY

M. leprae cannot be cultivated on artificial media, but can be grown with difficulty in nude mice and the nine-banded armadillo with a 14-day doubling time and at low temperatures (30–33°C). Recent sequencing of the *M. leprae* genome revealed that it has lost approximately one third of the genes possessed by *M. tuberculosis*. This confirms that *M. leprae* is well adapted to growth in humans (Cole et al, 2001).

Leprosy manifests in a spectrum of disease forms, ranging from the paucibacillary (PB) tuberculoid to the multibacillary (MB) lepromatous form (*Figure 1*) (Evans and Lockwood, 1999). Depending on the individual's immune response to

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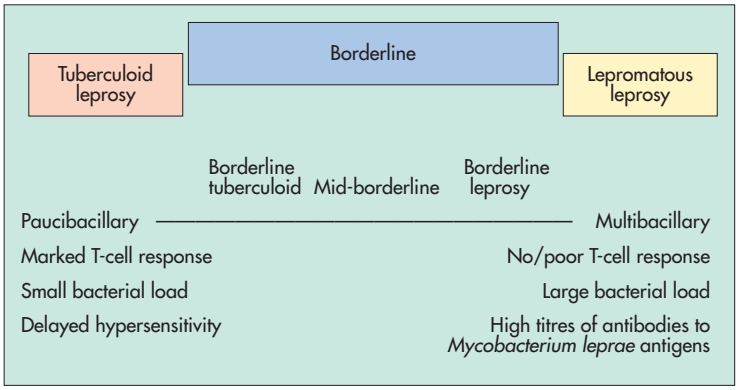

Figure 1. Leprosy — a spectrum of disease.

M. leprae infection, the disease will manifest at the tuberculoid or lepromatous end or as borderline disease. Immunologically, borderline cases are unstable, and polar tuberculoid and lepromatous cases are stable.

CLINICAL PRESENTATION

Patients present with either skin or nerve lesions or a combination of both. Leprosy only affects the peripheral nerves and never the central nervous system. Patients in the UK present in a variety of ways and thus to numerous specialists (*Table 1*), e.g. with skin lesions to a dermatologist, with neuropathy to a neurologist and with arthritis or scleritis to a rheumatologist. All types of leprosy are seen in the UK, therefore a patient may present with a macular hypopigmented skin lesion, weakness or pain in the hand as a result of nerve involvement, facial palsy, acute foot drop or blisters, or burns or ulcers as a result of neuropathy. Patients may also present with painful eyes as a first indication of lepromatous leprosy. Leprosy should be considered in all persons from leprosy endemic areas with typical skin lesions, neuropathic ulcers or a peripheral neuropathy (*Figures 2–4*).

DIAGNOSIS

Leprosy is a clinical diagnosis based on finding one or more of the following (Hastings, 1994) (*Table 2*):

1. Anaesthetic skin lesions
2. Peripheral nerve enlargement or impairment
3. Acid-fast bacilli on slit skin smears or skin biopsy.

TABLE 1.
Modes of presentation of leprosy in the UK

Referred specialist	Modes of presentation	Common differential diagnosis	Leprosy diagnosis
Dermatologist	Macular skin lesions	Vitiligo	All types of leprosy
		Pityriasis versicolor	
Dermatologist	Nodular skin lesions	Erythema nodosum	Erythema nodosum leprosum or lepromatous
		Sarcoid	
Dermatologist	Infiltrated skin lesions	Psoriasis	Type 1 reaction
		Lupus vulgaris	
Dermatologist	Leonine facies	Mycosis fungoides	Lepromatous leprosy
		Leukaemia	
Neurologist	Sensory impairment +/- muscle wasting	Diabetic neuropathy	All types of leprosy
		Syringomelia	
Neurologist	Claw hand	Trauma	All types of leprosy
		Dupuytren's contracture	
Neurologist	Collapsed bridge of nose	Wegener's granulomatosis	Lepromatous leprosy
		Congenital syphilis	
Neurologist	Foot drop	Trauma	All types of leprosy
		Friedreich's ataxia	
Neurologist	Facial paralysis	Bells' palsy	All types of leprosy
Rheumatologist	Arthritis	Rheumatoid arthritis	Lepromatous leprosy
		Connective tissue disorders	
Rheumatologist or orthopaedic surgeon	Neuropathic ulcers	Diabetes mellitus	All types of leprosy
		Raynaud's disease	
Rheumatologist or ophthalmologist	Scleritis/episcleritis	Rheumatoid arthritis	Erythema nodosum leprosum

Clinical examination

The patient's entire body should be examined in good light to look for hypopigmented areas, pink macules, infiltration (raised patches), nodules, burns, scars or ulcers. Reduction of sweating and hair growth should also be noted. All skin lesions should be tested with cotton wool or light touch for anaesthesia.

Peripheral nerves should be palpated to look for thickening or tenderness. Evidence of blisters, burns or ulcers may indicate sensory loss of a particular peripheral nerve. The sensory function of the peripheral nerves should be tested with cotton wool or pinprick. Sensory loss in an affected nerve is usually regional. In many leprosy programmes, sensory testing is carried out using different weighted monofilaments from 200 mg to 300 g but can be detected by any clinician using light touch or pinprick.

To examine the motor component of peripheral nerves, first observe for loss of muscle bulk, then examine for weakness. Power is assessed by the usual Medical Research Council 0–5 grading system (equivalent to voluntary muscle testing, the term used by leprosy workers).

Bacteriological examination

In a suspected case of leprosy, slit skin smears are taken to look for the presence of acid-fast bacilli. The number of *M. leprae* in the patient's lesions (bacterial index) is counted from the smears. However, smears should be taken and read by an experienced person. Outside specialist units, skin biopsies including the full depth of the dermis should be taken and sent for staining for acid-fast bacilli and histology in a suspected case of leprosy.

A negative slit skin smear does not exclude leprosy as tuberculoid lesions have no detectable bacteria.

Histological examination

Histopathological evaluation is essential for accurate classification of leprosy lesions, and it is probably the best diagnostic test in the UK, both for confirming and excluding the diagnosis of leprosy. The presence of granulomata and lymphocytic infiltration of nerves in anaesthetic skin lesions essentially confirms the diagnosis. If skin lesions are absent, a nerve biopsy from a cutaneous thickened nerve may be taken.

On request forms, it is always helpful to the pathologist to include information as to the ethnicity of the patient and the possibility of leprosy in the differential diagnosis.

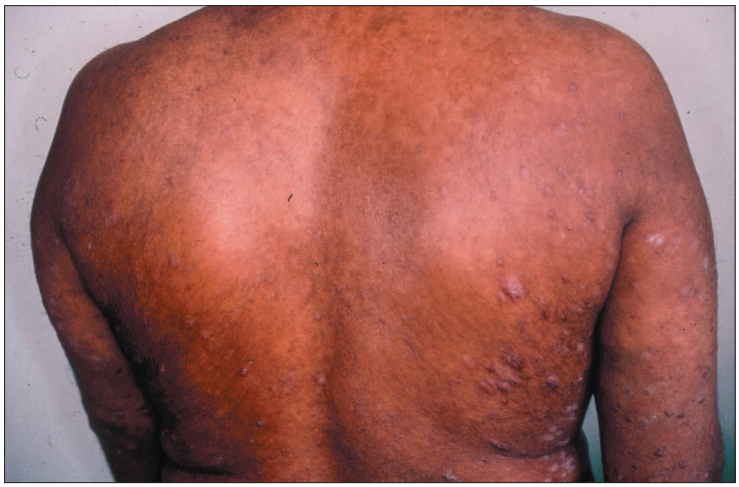

Figure 2. Untreated lepromatous leprosy.

Serological tests and polymerase chain reaction

There is no good serological test with adequate sensitivity and specificity for leprosy (Smith, 1992). Methods based on the polymerase chain reaction have been developed but have proved too insensitive and non-specific for general diagnostic use (Wichitwechkarn et al, 1995).

Figure 3. Lepromatous leprosy in a Nepali male: numerous small shiny erythematous macules.

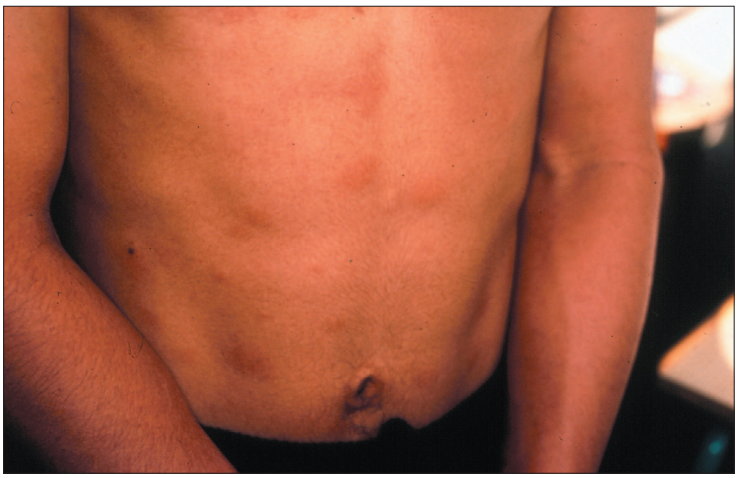

Figure 4. Borderline tuberculoid lesion in a Caucasian male: large irregular macule on forearm with well-defined edge. This hypopigmented area is anaesthetic, dry and hairless.

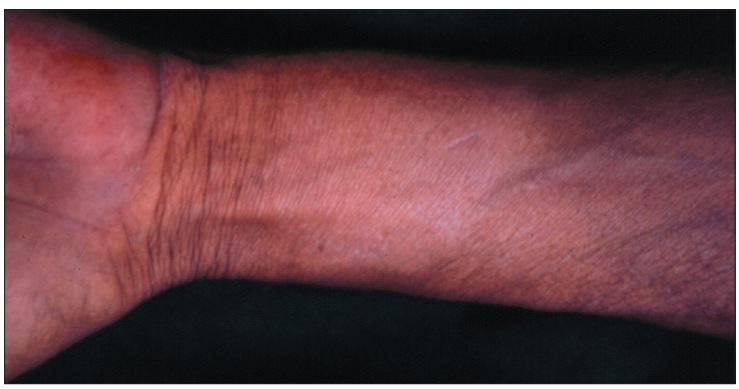

TABLE 2.
Characteristic features of different types of leprosy

	Tuberculoid	Borderline tuberculoid	Mid-borderline	Borderline lepromatous	Lepromatous
Skin lesions	Single, well-defined, hypopigmented, erythematous macule	Few, asymmetrical and well-demarcated macules	Few asymmetrical, less well-demarcated and shiny	Many symmetrical shiny macules, and plaques	Many symmetrical erythematous, shiny macules, papules and nodules
Sensory impairment in lesions	Marked	Marked	Moderate	Slight	Late glove and stocking neuropathy
Peripheral nerve involvement	Single peripheral nerve trunk	Several and asymmetrical	Multiple	Multiple and symmetrical	Multiple, late, symmetrical

REACTIONS

Leprosy is complicated by immunological phenomena called reactions. Reactions describe the sudden appearance of symptoms and signs of acute inflammation and occur in approximately 30% of leprosy patients. This occurs as a result of immune reactions against antigenic components liberated from the bacilli. Patients can present with reaction before treatment, and a significant proportion of patients develop reactions within the first 6 months of treatment. There is also an increase in the incidence of reactions in pospartum patients. However, reactions can occur after successful multidrug therapy (MDT) and are the result of persistence of the *M. leprae* antigen (Whitty and Lockwood, 1999).

There are two types of reactions (*Table 3*). Reversal reactions involve local skin and nerve inflammation only and erythema nodosum leprosum (ENL) presents as a systemic disease (*Figure 5*). A patient with ENL may be very sick with high temperatures, painful subcutaneous nodules, peripheral oedema and inflammation of the nerves, eyes, joints, muscles, bones and testes. Patients may suffer from recurrent reactions or repeated reactions after treatment, resulting in increased suffering and disability.

TREATMENT

Treatment of infection

Leprosy is treated with MDT, which is a combination of dapsone, rifampicin and clofazimine. This was introduced by WHO in 1982, and it is very successful with a high cure rate, few side-effects and low relapse rates. The relapse rate following a full course of MDT is 1%/year. The benefits of MDT include the prevention of drug resistance and a fixed duration of therapy, leading to better patient compliance.

Dapsone was first introduced as monotherapy in the 1940s, but drug resistance soon developed. The addition of clofazimine in the

TABLE 3.
Leprosy reactions

Reaction	Immune response	Type of leprosy patient affected	Clinical features	
Reversal reactions	T-cell mediated	Borderline tuberculoid, mid-borderline and borderline lepromatous	Skin lesions	Erythema
				Swelling
				Tenderness
			Peripheral nerve lesions	Pain/tenderness
				Increased weakness
				Increased sensory loss
Erythema nodosum leprosum	Immune complex deposition	Borderline lepromatous and lepromatous	Skin lesions	Transient crops of small, painful, red nodules, lasting 2–3 days
			Other signs	Fever
				Malaise
				Lymph node enlargement
				Arthritis
				Iritis
				Orchitis
				Neuritis

1960s helped to combat resistance, but it was not until the introduction of rifampicin that the treatment was truly effective. Dapsone is bacteristatic and a competitive inhibitor of para-aminobenzoic acid as well as interfering with folate metabolism. Side-effects are rare with dapsone and include mild haemolysis and an allergic rash, occurring in the first few months of treatment.

Rifampicin is bactericidal and the most effective anti-leprosy drug, rendering the patient non-infectious within 72 hours of commencing therapy. There have been few serious side effects related to rifampicin, which may be because of its monthly dose. The monthly rifampicin dose for leprosy is equivalent to the daily dose for antituberculous therapy. No cases of resistance have been recorded.

Clofazimine has an action similar to dapsone and is also an anti-inflammatory agent. The main problem encountered with clofazimine is increased skin pigmentation and dryness. This icthyosis is reversible and slowly resolves on stopping clofazimine.

MDT is safe in pregnancy and in breastfeeding mothers. Children should receive reduced doses of the drugs. MDT is a time-limited treatment (*Table 4*). Field workers review patients and supervise the taking of the monthly medication.

Treatment of nerve damage

Patients may present with nerve damage or develop nerve impairment during or after MDT. Patients presenting with new nerve damage of less than or equal to 6 months duration should be treated with corticosteroids in addition to their MDT. Nerve damage refers to peripheral sensory or motor neuropathy. The dosage of oral prednisolone is started at 40 mg daily and reduced over 4–6 months depending on clinical response.

Treatment of reactions

This is currently the most challenging problem. For reversal reactions, patients can be started on doses as high as 60 mg of prednisolone and tapered over several months to try to prevent further nerve damage.

ENL is difficult to treat. For mild reactions, non-steroidal anti-inflammatory drugs can be used. For more severe cases, steroids and high dose clofazimine are used. For very severe cases and those unresponsive to corticosteroids, thalidomide can be used, but not in women of childbearing age. Thalidomide is the most effective drug for ENL, but it is not widely available in all leprosy endemic countries, and in some countries, it can only be administered on an inpatient basis.

All cases of reactions should be referred for specialist management as soon as the diagnosis is suspected.

ONGOING MANAGEMENT

Prevention of infection

At present, there is no specific vaccine to prevent infection by *M. leprae,* although there is good evidence that bacille Calmette-Guérin (BCG) has protective efficacy. Nevertheless, this can be variable. Adding *M. leprae* antigen to BCG does not increase the efficacy of BCG.

Prevention of complications

Infection of peripheral nerves with *M. leprae* will lead to a peripheral neuropathy if not treated appropriately. Secondary complications occur as a result of the neuropathy (*Figure 6*). In the hands and feet, injuries, burns, cuts and pressure sores may lead to secondary bacterial infection, cellulitis and osteomyelitis. Autonomic neuropathy causes dry skin, which may lead to fissures, ulceration, scarring and ultimate deformity and disability. Education is essential for all patients and health providers to prevent secondary complications and consists of:

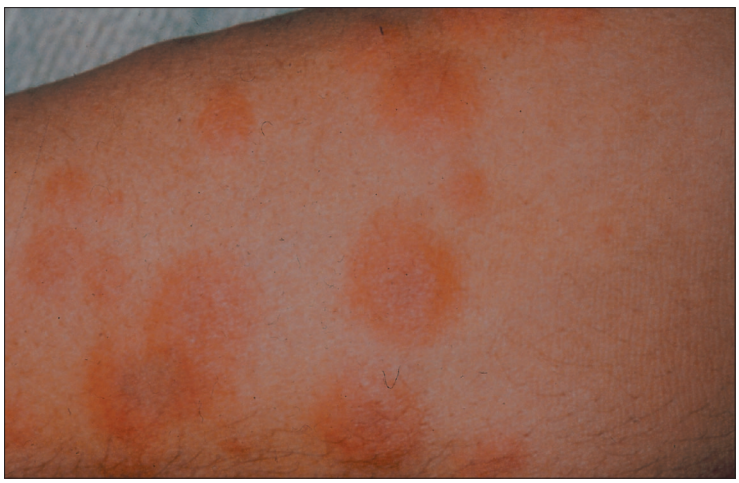

Figure 5. Tender nodules in erythema nodosum leprosum.

TABLE 4.
Multidrug therapy regimen

Regimen	Drug	Dosage	Frequency	Duration
Paucibacillary	Rifampicin	600 mg	Monthly (supervised)	6 months
	Dapsone	100 mg	Daily (self-administered)	
Multibacillary	Dapsone	100 mg	Daily (self-administered)	2 years
	Clofazimine	50 mg	Daily (self-administered)	
	Clofazimine	300 mg	Monthly (supervised)	
	Rifampicin	600 mg	Monthly (supervised)	

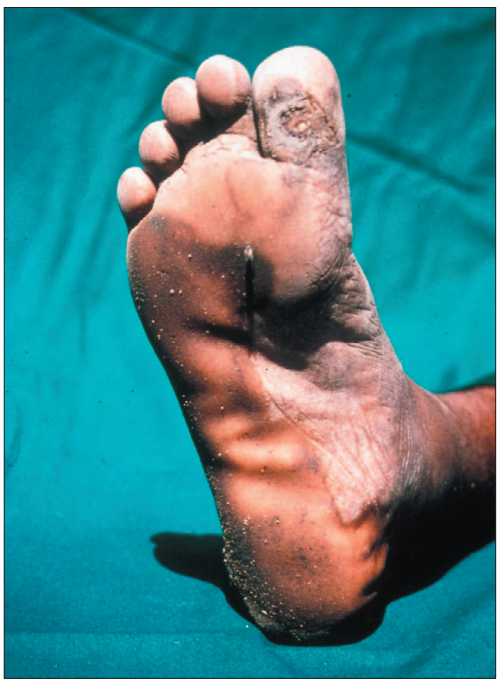

Figure 6. Neuropathic ulcer post-tibial lesion.

- Education about the basics of leprosy — what it is, how it is caught, how infectious it is
- What the treatment is — its effectiveness and side effects
- How to prevent injuries and complications
- How to care for the anaesthetic limb — e.g. comfortable footwear and cessation of smoking
- Education about reactions and how to recognize them.

Psychosocial aspects

Leprosy is a cruel disease not only because of the physical deformities a patient can be left with but also because, even now, it is still associated with a great deal of stigma.

Stigmatization results in delayed presentation to health services and poor compliance with follow-up and further management. There is huge psychological damage to the patient, and depression is a common occurrence. As one patient at the Hospital of Tropical Diseases commented:

'Leprosy is worse than AIDS and cancer from a stigma viewpoint, as these diseases are now accepted and patients will receive support not revulsion from society.'

Health professionals and the public have to be educated that this disease is curable and that cured individuals pose no threat to the health of their associates.

CONCLUSION

Although MDT is effective in curing the active infection, leprosy is far from eradicated. There is no vaccine to prevent infection, symptoms may present years after the primary infection, stigma may lead to delayed presentation, diagnosis and treatment may be delayed because of medical ignorance and patients cured of infection may develop severe and recurrent reactions.

Leprosy is being diagnosed late in the UK. Any patient with peripheral nerve damage and/or skin signs, especially if originally from a developing country, should always have leprosy considered in the differential diagnosis. HM

Conflict of interest: none.

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KEY POINTS

- Leprosy is a clinical diagnosis of skin lesions, neuropathic ulcers or neuropathy.
- Approximately one new case of leprosy is diagnosed in the UK every month.
- Of new UK cases, 40% have functional impairment as a result of sensory loss.
- Early diagnosis and treatment results in cessation of infectivity and cure.
- Leprosy must be considered in an individual from an endemic country with skin lesions or nerve impairment.