Leprosy

Synonym: Hansen's disease

This disease is notifiable in the UK - see **NOIDs** article for more detail.

Leprosy is an infectious disease caused by an obligate intracellular bacillus *Mycobacterium leprae*. Although rarely seen in the UK, leprosy is one of the most common causes of peripheral neuropathy worldwide. The first descriptions of leprosy are from India around 600 BC. In the fourth century, the disease was imported into Europe, where its incidence peaked in the 13th century. Armauer Hansen discovered *M. leprae* in Norway in 1873. It was the first bacillus to be associated with human disease.

Pathogenesis

- The intracellular mycobacteria act on the Schwann cells producing a chronic granulomatous reaction resulting in the destruction of both myelin and the underlying nerve cells.The damage to nerves and their protective outer layers leads to permanent neurological damage.
- Progress has now been made in culturing the organism, defining its genomic sequence, and understanding the important differences in the host's reaction to the organism.
- The mode of transmission of the disease is uncertain, although it is thought that droplet transmission, contact with infected soil and contact with infected blood all occur.
- The severity of disease which develops in any individual is now known to be due to the immune response of that individual to the organism. Genetic susceptibility to leprosy has been observed in some races and is thought to reflect a difference in immunological response to the mycobacterium.

The spectrum of clinical manifestations is correlated with the level of cell-mediated immunity[1]:

- Tuberculoid leprosy is characterised by restricted growth of the pathogen and high cell-mediated immunity.
- At the other end of the spectrum is lepromatous leprosy, in which the cell-mediated immunity is very ineffective and so there is a widespread dissemination of the bacilli.
- Between tuberculoid and lepromatous leprosy, the borderline group can be divided into three subgroups: borderline tuberculoid, borderline-borderline and borderline lepromatous.

Epidemiology

- The reported prevalence of leprosy has declined, in part due to a World Health Assembly initiative aimed at the elimination of leprosy as a public health problem.
- In 2002 the World Health Organization (WHO) reported a prevalence of 1 per 10,000 as opposed to 12 per 10,000 15 years earlier[2].
- Significant improvements in leprosy control have occurred, but leprosy remains a public health problem in many countries due to its high incidence and rate of transmission[3].
- The majority of cases are now centred in Southeast Asia, Africa and South America, with 64% of all cases occurring in India.

Presentation

- The symptoms of leprosy may develop in a very insidious fashion due to an average incubation period of approximately seven years.Three features are required in order to make a diagnosis of leprosy:
    - Reddish patches or hypopigmented areas of skin with reduced sensation.
    - Thickened peripheral nerves.
    - The presence of acid-fast bacilli in skin smears or biopsies.

- The initial skin lesion, often referred to as indeterminate leprosy, may resolve spontaneously. If this fails to happen, the subsequent progression of the disease will depend on the patient's immune response to the organism.
- Lepromatous leprosy, in which there is a high bacterial load and diffuse infiltration, can affect not only the skin, but also areas such as the respiratory tract, the eye and lymph glands [4].
- The mycobacterium has a preference for cooler temperatures and therefore it is the superficial structures rather than deep visceral organs which are usually involved.
- Features which may be seen in leprosy include:

    - **Skin lesions** - hypopigmented macules and plaques (common), papules and nodules (rare)
    - **Neurological involvement** - damage to small nerves to the skin, producing reduced sensation and anhidrosis, or peripheral nerve damage with the posterior tibial nerve being most commonly affected followed by ulnar, median, lateral popliteal and facial [2]. Peripheral nerve damage may result in a 'glove and stocking' pattern of sensory loss and/or a distal weakness beginning with the intrinsic muscles of the hands and feet.
    - **Ocular involvement** - damage to the eye resulting in blindness may occur as a combination both of nerve damage and direct infiltration of the eye with the organism. Damage to the trigeminal nerve may also result in reduced blink rate and impaired corneal sensation resulting in injury and ulceration to the cornea.
    - **Systemic involvement** - severe forms of lepromatous leprosy may be associated with systemic disease affecting, for example, the respiratory tract (both upper and lower), the testes, lymph nodes, kidneys and bones. They may also (rarely) cause amyloidosis.

Differential diagnosis

Other neurological disorders that share similar features to leprosy will need to be considered in the differential diagnosis such as [5]:

- Mononeuritis multiplex
- Syringomyelia
- Other causes of neuropathy - eg, diabetes mellitus

Investigations

- The gold standard for establishing the diagnosis of leprosy, is the finding of *M. leprae* in biopsies of the skin lesions or slit skin smears.
- Important serological tests for the detection of *M. leprae* antibodies or antigens are fluorescent antibody absorption (FLA-ABS) test and phenolic glycolipid-1 (PGL-1) ELISA.
- In patients with pure neural leprosy, serum levels of PGL-1 may be helpful.
- Patients seropositive for PGL-1 have an increased risk of relapse, and the level of PGL-1 may be used as an indicator of bacterial load in these patients.
- Nerve conduction studies may be useful in both establishing the diagnosis, and in monitoring the disease progress or response to treatment.

Classification

There are two different classification systems for leprosy.

Paucibacillary or multibacillary leprosy

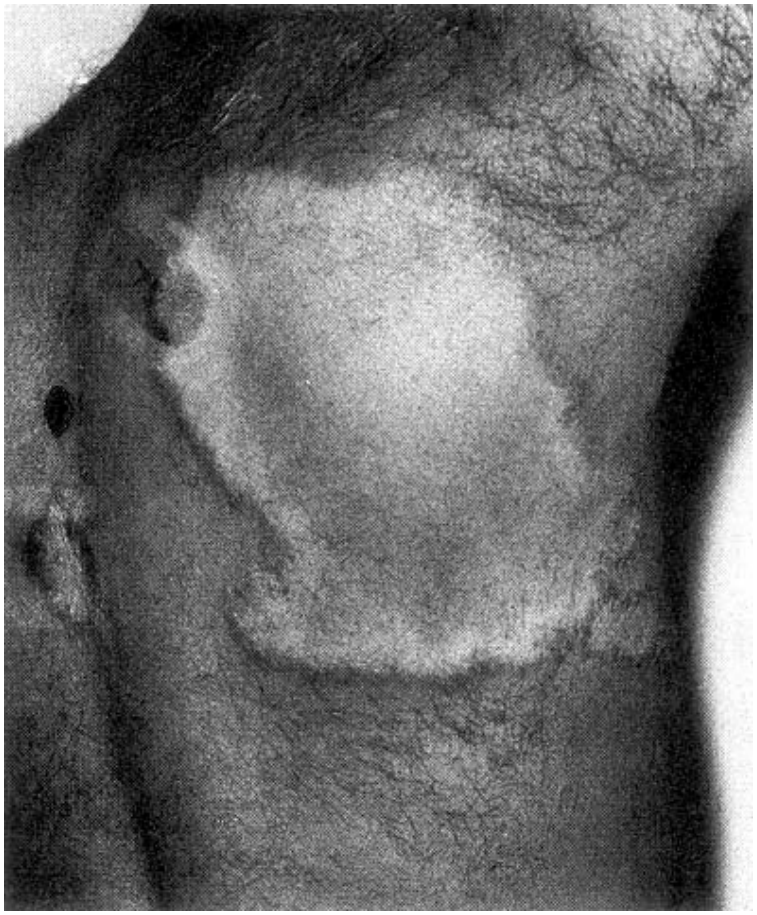
- Paucibacillary leprosy - negative smears at all sites; single or only a few hypopigmented and hypo-aesthetic skin lesions.
- Multibacillary leprosy - either positive smears at any site, or multiple (>5) hypopigmented, hypoanaesthetic or erythematous skin lesions (sometimes poorly defined). Lesions may also be macules, papules or nodules.

Tuberculoid or lepromatous leprosy

After exposure to leprosy and the incubation period, leprosy may fluctuate between various stages depending on the individual's cell-mediated immune response or in response to therapy.

Transition toward the tuberculoid leprosy (TT) end of the spectrum is referred to as upgrading (and may lead to a reversal or type I reaction) and transition toward the lepromatous leprosy (LL) pole as downgrading:

- Indeterminate stage - single skin lesion, frequently heals spontaneously.
- Tuberculoid leprosy (TT) - few skin lesions.
- Borderline tuberculoid leprosy (BT).
- Borderline leprosy (BB).
- Borderline lepromatous leprosy (BL).
- Lepromatous leprosy (LL) - most severe stage, diffuse skin lesions and high bacterial load.



Tuberculoid leprosy

Management

- This involves the use of effective antimicrobial drugs but also includes treatment of immune reactions and nerve damage[6].

- Reduction in social stigma associated with disease at global, national and local levels increases self-reporting and allows timely intervention[7].
- Specialist advice is available in the UK from a member of the Panel of Leprosy Opinion at the Department of Health.

General measures

Notification

- In the UK, all cases of leprosy must be notified under the Public Health (Infectious Diseases) Regulations, 1988[8].
- Case reports are maintained on a central confidential register at the Communicable Disease Surveillance Centre.

Staff and services

- Leprosy diagnosis and treatment are currently highly centralised activities, often conducted only by specialised staff[7].
- To achieve long-term success, leprosy control must be incorporated into national public health services[7].
- The geographical coverage of leprosy services must also be expanded to improve access to local health facilities.
- Community healthcare staff must be well trained to enable them to diagnose accurately and to manage leprosy[7].

Education

- Leprosy is feared because of the associated deformities and social stigma. Fear of contagion also contributes to the enforced isolation of leprotic patients.
- Mass campaigns are needed to stimulate public awareness of the disease and its cure. Remote communities, in particular, need access to information to reduce prejudice and stigmatisation[7].
- People must accept leprosy as a simple curable disease and be aware of the availability of free and effective treatment.

- Patient education can also prevent neuropathic sequelae and improve compliance with medication.

Early detection

- Early detection and treatment are essential for prevention of nerve damage[6].
- Many patients delay seeking treatment until they have infected many contacts and developed irreversible deformities and disability.
- Public health initiatives must change the negative perception of leprosy and encourage people to come forward for treatment as soon as possible[7].

Rehabilitation

- Assessment and monitoring of peripheral nerve function should be an integral component of the routine assessment of every patient[6].
- After drug treatment or surgery, physical rehabilitation and attention to the social and psychological well-being of patients with disabilities are essential to facilitate re-integration into society.

Antileprotic chemotherapy

Drug treatment aims to reduce morbidity and prevent complications.

Multidrug therapy (MDT)

- The introduction of MDT by the WHO has produced dramatic changes in public control programmes and the management of leprosy.
- MDT is now available free to all leprosy patients throughout the world[7].

Schedule for treatment of multibacillary leprosy
A three-drug regimen is recommended for multibacillary leprosy (lepromatous, borderline-lepromatous and borderline leprosy). The following regimens are used, with minor local variations:

- Rifampicin (monthly), dapsone (daily) and clofazimine (300 mg monthly and 50 mg daily).

- Multibacillary leprosy should be treated for at least two years.
- Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum leprosum) reactions.
- During reversal reactions neuritic pain or weakness can indicate the rapid onset of permanent nerve damage.
- Treatment with prednisolone should be started immediately.
- Mild type II reactions may respond to aspirin. Severe type II reactions may require steroids.
- Thalidomide may be used for patients who have become dependent on steroids but should only be used only under specialist supervision.

Schedule for treatment of paucibacillary leprosy
A two-drug regimen is used for paucibacillary leprosy (borderline-tuberculoid, tuberculoid, and indeterminate). The following regimens are used, with minor local variations:

- Rifampicin (monthly) and dapsone (daily).
- Paucibacillary leprosy should be treated for six months.

Efficacy of multidrug therapy

- Patients are non-infectious soon after the first dose of MDT and so further transmission of disease is prevented [7].
- MDT regimens produce good clinical responses, and relapse rates following completion of scheduled courses of therapy are very low [6].
- Relapse rates are approximately 0.06% per year for multibacillary leprosy and 0.1% per year for paucibacillary leprosy [7].
- The WHO estimates that early detection of disease and effective treatment have prevented disabilities in four million people, thus preventing significant social and economic losses.
- The MDT is established as a highly cost-effective health intervention [7].

Other drugs

- Second-line antileprotic drugs can be used for patients intolerant of first-line therapy. Treatment should be under direct supervision at a specialist centre[7].
- A monthly combination of rifampicin, ofloxacin and minocycline has been used for multibacillary and paucibacillary disease with good clinical outcomes. However the long-term relapse rates are unknown and so close follow-up is essential[6].
- Single-dose therapy using rifampicin, ofloxacin and minocycline is in use worldwide as alternative treatment of single-lesion paucibacillary leprosy.
- Both multiple-dose MDT and single-dose treatment achieve high cure rates but multiple-dose therapy achieves higher long-term cure rates and is therefore still the treatment of choice in the UK.

Drug resistance

- For many years dapsone was the only effective antileprotic drug available. Its long-term use as monotherapy led to selection of dapsone-resistant *M. leprae*[7].
- MDT was introduced specifically to prevent the emergence of further drug resistance, particularly against rifampicin[7]. No resistance to the recommended MDT regimen has yet been documented.
- However, resistance to multiple antileprotic drugs has been detected among patients receiving non-standardised treatment. Drug susceptibility testing is thus recommended in cases of relapse, where inadequate initial treatment is suspected[9].

Other management issues

- Corticosteroids are used for treating acute nerve damage in leprosy but evidence from randomised controlled trials does not show a significant long-term effect[10].
- Decompressive surgery is used for treating nerve damage in leprosy but there is no evidence to show a significant added benefit of surgery over steroid treatment alone[11].

- Nerve decompression is indicated when signs of peripheral nerve entrapment have not resolved after 3-4 weeks of steroid therapy and if there are signs of nerve abscess or chronic entrapment.
- Peripheral nerve reconstruction may help restore sensation to the hands and feet and nerve grafts may be helpful for patients with localised nerve lesions.
- Arthrodesis or tenodesis may be necessary to correct clawing or stabilise joints and chronically diseased limbs may even require amputation.
- Cosmetic surgery may be effective for nasal reconstruction, replacement of eyebrows or excision of redundant earlobe or eyelid skin.

Management of reactions

- Immune-mediated reactions occur secondary to changes in the host's immune status and may occur before diagnosis, during treatment or after cure[6].
- Full-dose MDT should be continued throughout all reversal reactions with the addition of anti-inflammatory therapy, analgesia and physical support as necessary.
- Type I or reversal reactions are associated with an increase in cell-mediated immunity. Early detection is essential to avoid irreversible peripheral nerve damage. The frequency of such reactions is increased during the early stages of treatment of multibacillary leprosy[7].
- Type I reactions should be treated immediately with high-dose prednisolone. Rest and the timely use of splints and physiotherapy are also recommended.

- Erythema nodosum leprosum:

    - Type II or erythema nodosum leprosum (ENL) reactions are systemic inflammatory responses to the deposition of extravascular immune complexes.
    - The frequency and severity of ENL reactions are significantly reduced in patients on MDT but may still occur during or after treatment [7].
    - Severe ENL reactions also require corticosteroids but mild reactions may respond to aspirin or chloroquine.
    - Thalidomide has been used successfully in the management of ENL reactions, for men and postmenopausal women. Its role is limited by teratogenicity and must only be used under specialist supervision [12].

Pregnancy

- Hormonal and immunological changes during pregnancy cause suppression of cell-mediated immunity and worsening of symptoms. Infants born to mothers with leprosy have low birth weights and an increased risk of developing the disease.
- The WHO therefore recommends that MDT be continued during pregnancy. However, the drugs used in the treatment of leprosy are not without risk and treatment should be under specialist supervision.
- Rifampicin reduces the efficacy of hormonal contraceptives, so alternative contraceptive advice should be offered [13].
- High doses of rifampicin may be teratogenic and it is not recommended for use during the first trimester.
- Dapsone may cause neonatal haemolysis and methaemoglobinaemia. If necessary it should be prescribed to pregnant women in combination with folic acid.
- Clofazimine may cause discoloration of the skin of breast-fed infants.

- The use of thalidomide remains strictly contra-indicated in women of childbearing potential.

Chemoprophylaxis

- Close leprosy contacts who are treated with rifampicin have lower rates of subsequent disease [14].
- Other studies of leprosy chemoprophylaxis for contacts of index cases have failed to show any significant protection.
- The WHO does not currently recommend the routine use of chemoprophylaxis but suggests that contacts should simply be monitored for signs or symptoms suggestive of disease.

Future treatments

- Pentoxifylline and clofazimine have shown encouraging results for the treatment of severe type II immune reactions and are currently undergoing large clinical trials.
- Mycobacterium w (Mw) vaccine has shown reasonable efficacy in eliciting immunoprophylactic responses in household contacts of leprosy patients, particularly in children [15].
- Therapeutic roles for leprosy vaccines and other immunomodulatory agents are also under investigation. It is believed that enhancement of defective host cell-mediated immunity improves clearance of mycobacteria.
- However, the use of immunotherapy in the treatment of established leprosy is currently hampered by an increased frequency of type I reactions.

Complications

- If left untreated, leprosy may result in blindness and physical deformity.
- Despite treatment with MDT, reactive states may still lead to neurological damage producing Charcot's joints and other deformities.

- Secondary amyloidosis is now rare in patients treated with MDT.

Prognosis

- The prognosis for patients adequately treated with MDT is very good.
- Relapse with MDT is 0.1% per year for paucibacillary leprosy and 0.06% per year for multibacillary leprosy on average, with a low frequency of adverse effects.
- Relapse may occur as late as thirteen years after treatment; however, a second course of MDT is likely to produce a good response.
- Nerve damage may still occur in a few, despite appropriate treatment, due to a reactive state.

Prevention

- Prevention of leprosy by vaccination would provide a valuable public health tool. However, there is currently no specific vaccine effective against leprosy[7].
- The bacillus Calmette-Guérin (BCG) vaccine was originally aimed at prevention of tuberculosis but is actually more effective against leprosy[7]. The efficacy of the BCG vaccination against both tuberculosis and leprosy is hugely variable, depending on the study population.
- The BCG vaccine generally offers 40-50% protection against leprosy[7]. The addition of killed *M. leprae* to the BCG vaccine is believed to increase its efficacy.
- The International Committee of the Red Cross (ICRC) bacillus vaccine provided 65-70% protection in efficacy trials in India. It is considered to be the most effective vaccine against leprosy and is associated with few adverse effects.
- None of these vaccines has provided a reproducible level of efficacy that could be considered for a cost-effective worldwide public health strategy and they are not recommended by the WHO[7].

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