Leprosy
Diana N J Lockwood

Leprosy is a chronic, granulomatous disease caused by *Mycobacterium leprae*. The principal manifestations are skin lesions and peripheral neuropathy, and medical complications are caused by nerve damage, immunological reactions and bacillary infiltration. Drug treatment is effective in killing bacilli, but does not prevent nerve damage. In the UK, leprosy is a notifiable disease.

**Epidemiology**

Worldwide, leprosy continues to be a problem. There are about 650,000 new cases per year, 70% of which are in India. In all new cases seen in the UK, infection was acquired overseas. HIV infection is not a risk factor for the development of leprosy, but may worsen leprous neuritis.

**Transmission**

Untreated lepromatous individuals discharge bacilli from the nose. Infection occurs through the nose followed by haematogenous spread to skin and nerve. The incubation period is 2–5 years in tuberculoid disease and 8–12 years in lepromatous disease.

**Pathology**

*M. leprae* cannot be grown in vitro; nude mice and nine-banded armadillos are the best animal models. The genome of *M. leprae* has been completely sequenced. Bioinformatic analysis shows 165 unique genes, analysis of which will be vital for the development of new diagnostic tests and increased understanding of the disease.

*M. leprae* has a predilection for Schwann cells and skin macrophages. The patient’s immune response determines the features

<table>
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<th>What’s new?</th>
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<tr>
<td>• When added to antibacterial therapy, corticosteroids can reverse early nerve damage</td>
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<tr>
<td>• The genome of <em>M. leprae</em> has been sequenced</td>
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cellular anergy towards *M. leprae*, resulting in abundant bacillary multiplication. Between these two poles is a continuum, varying from moderate cell-mediated immunity (borderline tuberculoid), through true borderline, to little cellular response (borderline lepromatous).

**Neuropathy** – in skin lesions, the small dermal sensory and autonomic nerve fibres are damaged, causing local sensory loss and loss of sweating. Damage to peripheral nerves leads to regional sensory loss and dysfunction of muscles supplied by the affected nerve.

**Immunology**

Both T cells and macrophages are involved.

**Tuberculoid leprosy** – in these patients, lymphocytes respond to *M. leprae* antigens in vitro. Skin tests with lepromin (a soluble *M. leprae* sonicate preparation) elicit strongly positive responses. Tuberculoid patients have a Th1-type response to *M. leprae*, producing interleukin-2 (IL-2) and interferon-γ (IFNγ). This strong cell-mediated response clears antigen, but with concomitant local tissue destruction.

**Lepromatous leprosy** – these patients have specific cell-mediated anergy to *M. leprae* and their lymphocytes do not respond to *M. leprae* antigens in vitro. They are unresponsive to intradermal challenge with lepromin. Lepromatous patients exhibit specific T cell failure and macrophage dysfunction, with defects in production of IL-2 and IFNγ; they produce Th2-type cytokines.

**Immune-mediated reactions:** acute immune-mediated reactions are a serious complication of leprosy.

**Type 1 reactions** are episodes of delayed hypersensitivity occurring at sites of localization of *M. leprae* antigens.

**Type 2 reactions** – erythema nodosum leprosum results from immune complex deposition.

**Clinical features**

The signs of leprosy (Figure 1) are:

- skin lesions, typically anaesthetic at the tuberculoid end of the spectrum
- thickened peripheral nerves
- acid-fast bacilli on skin smears or biopsy.
Peripheral nerves are vulnerable at sites where they are superficial or lie in fibro-osseous tunnels. The nerves most often involved are the ulnar (elbow), median (wrist), radial cutaneous (wrist), common peroneal (knee), posterior tibial and sural (ankle), facial (crossing the zygomatic arch) and great auricular (posterior triangle of the neck). Affected nerves may be enlarged and tender.

Blindness is a devastating complication of leprosy in patients with anaesthetic hands and feet. Eyelid closure is impaired when the facial nerve is affected. Damage to the trigeminal (Vth) nerve causes anaesthesia of the conjunctiva and the cornea, which is then susceptible to trauma and ulceration.

**Tuberculoid leprosy** (Figure 2) has a good prognosis. It may self-heal, and peripheral nerve damage is limited.

**Borderline tuberculoid** (Figure 3) – the skin lesions are similar to those in tuberculoid leprosy, but more numerous. Peripheral nerve damage may be widespread and severe. Patients are prone to type 1 reactions with consequent nerve damage.

**Borderline leprosy** is unstable; patients have numerous skin lesions varying in size, shape and distribution. Annular lesions with a broad, irregular edge and a sharply defined, punched-out centre are characteristic. Nerve damage is variable.

**Borderline lepromatous leprosy** is characterized by widespread, small macules (Figure 4). Patients may experience type 1 and type 2 reactions. Peripheral nerve involvement is widespread.

**Lepromatous leprosy** – patients with untreated polar lepromatous leprosy may be carrying 10^11 M. leprae. The earliest lesions are ill-defined (Figure 5). Gradually, the skin becomes infiltrated and thickened. Facial skin thickening leads to the characteristic leonine facies. Dermal nerves are destroyed, sweating is lost and ‘glove-and-stocking’ neuropathy is common. Nerve damage to large peripheral nerves occurs late in the disease. Nasal symptoms may be prominent as a result of bacterial invasion of the nasal mucosa. The pathognomonic collapse of the bridge of the nose results from bacillary destruction of the bony nasal spine. Testicular atrophy is caused by diffuse infiltration and the acute orchitis that occurs with type 2 reactions. This results in azoospermia and gynaecomastia.

Diagnosis

Diagnosis is clinical, by the finding of a cardinal sign of leprosy, and is supported by acid-fast bacilli in slit-skin smears or typical histology on skin biopsy. Skin biopsy reviewed by an experienced histopathologist is invaluable in classifying the patient and excluding other diagnoses. Skin lesions should be tested for anaesthesia. The peripheral nerves should be palpated for thickening and tenderness. There are no serological tests that detect leprosy across the spectrum. Polymerase chain reaction analysis for M. leprae DNA has not been developed as a diagnostic tool.

Doctors often fail to diagnose leprosy outside areas where leprosy is endemic. Patients may present with skin lesions, neuritis, arthritis, or ulcers secondary to neuropathy. Always consider leprosy as a possible cause of peripheral neuropathy or neuropathic ulcers in patients of Indian or African origin.

**Differential diagnosis** – leprosy is the most common cause of peripheral nerve thickening. Uncommon conditions such as Charcot–Marie–Tooth disease and amyloid are differentiated from leprosy by the absence of skin lesions and acid-fast bacilli. The anaesthesia of tuberculoid and borderline tuberculoid lesions differentiates them from other conditions resembling leprosy (e.g. vitiligo, mycotic skin infections).

Management

**Chemotherapy** – the WHO recommendations for chemotherapy of leprosy are listed in Figure 6. First-line antileprotic drugs are rifampicin, dapsone and clofazimine. Any patient with acid-fast bacilli on skin smear or biopsy should be treated for multibacillary disease. Patients with high bacterial loads (on skin biopsy or slit-skin smear) need treatment with multi-drug therapy for at least 24 months. Clinical improvement is rapid and toxicity is uncommon. Relapse rates are about 1%. Ofloxacin and minocycline are bactericidal for M. leprae and can be used as second-line agents. A single-dose, triple-drug combination (rifampicin, ofloxacin and minocycline) has been used in patients with single skin lesions.

**New nerve damage** – any patient with motor or sensory loss of less than 6 months’ duration should receive a 6-month course of oral corticosteroids as for the treatment of type 1 reactions (see below).
BACTERIAL TROPICAL INFECTIONS

WHO recommended multi-drug regimens for leprosy

<table>
<thead>
<tr>
<th>Type of leprosy</th>
<th>Monthly supervised</th>
<th>Daily self-administered</th>
<th>Duration of treatment</th>
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<tbody>
<tr>
<td>Paucibacillary</td>
<td>Rifampicin, 600 mg</td>
<td>Dapsone, 100 mg</td>
<td>6 months</td>
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<tr>
<td></td>
<td>Clofazimine, 300 mg</td>
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<tr>
<td>Multibacillary</td>
<td>Rifampicin, 600 mg</td>
<td>Clofazimine, 50 mg</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>Dapsone, 100 mg</td>
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Patients with a high bacterial load may need treatment for at least 24 months

Advice on leprosy

In the UK, members of the Department of Health Panel of Leprosy Opinion are available for consultation by medical staff and patients at any time, for help with diagnosis and management; contact the Hospital for Tropical Diseases, London (tel: 020 7387 9300)

Patient education is vital. Patients must be reassured that, within a few days of chemotherapy, they will no longer be infectious and can lead a normal social life. It should be emphasized that care and awareness of their limbs is as important as chemotherapy.

Preventing disability – nerve damage produces anaesthesia, dryness and muscle weakness, which lead to misuse of the affected limb and resultant ulceration, infection and, ultimately, severe deformity. Dryness predisposes to cracking of the skin and secondary infection; it can be alleviated by soaking the feet and applying oil-based creams. Physiotherapy can prevent contractures, muscle atrophy and over-stretching of paralysed muscles.

Immune-mediated reactions – type 1 reactions occur in borderline leprosy (Figures 7 and 8). Skin lesions become erythematous, and peripheral nerves tender and painful. Loss of nerve function can be sudden; foot-drop can occur overnight.

Type 2 reactions occur in borderline lepromatous and lepromatous patients and manifest with malaise, fever and crops of small, pink nodules on the face and limbs. Iritis and episcleritis are common. Other signs are acute neuritis, lymphadenitis, orchitis, bone pain, dactylitis, arthritis and proteinuria. Erythema nodosum leprosum may continue intermittently for several years. Principles of management of immune-mediated reactions are:

• control the acute inflammation and ease the pain
• treat the neuritis
• halt eye damage.

Type 1 reactions should be treated using prednisolone, 40 mg/day p.o. initially reduced by 5 mg/day each month. Erythema nodosum leprosum is difficult to treat, requiring high-dose corticosteroids (prednisolone, 80 mg daily tapered rapidly) or thalidomide. The chronicity of type 2 reactions makes corticosteroid dependency a problem. Thalidomide is effective in controlling erythema nodosum leprosum, but is problematic in women of child-bearing age because of teratogenic side-effects in early pregnancy.

Vaccines – there is no specific vaccine against leprosy, but several trials have shown BCG to be protective.

FURTHER READING