

Leprosy - A Review

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ABSTRACT

Leprosy is divided into paucibacillary and multibacillary types, depending on whether bacilli are present in the skin smear. In tuberculoid leprosy, a strong cell-mediated immune response results in isolated lesions and histologically granulomatous lesions where no bacillus is present. In lepromatous leprosy, poor cell-mediated immunity results in diffuse lesions in which numerous bacilli are present. Low-dose dapsone monotherapy led to the development of dapsone resistance in the 1970s; but with the introduction of WHO multi-drug therapy, the incidence of leprosy has declined dramatically. There have been relapses both after dapsone monotherapy and WHO multi-drug therapy. Persisting organisms have been found even after high dose regimen and in clinically cured patients. Continual surveillance is therefore important. Promising new drugs include minocycline, sparfloxacin, and clarithromycin.

Keywords: leprosy, persisting organisms, multi-drug therapy

INTRODUCTION

Leprosy is caused by the organism *Mycobacterium leprae*. It is one of the oldest diseases recorded. There had been bony changes of leprosy in skeletons dating to the second century B.C. Evidence suggested that it spread east from India to China at around 500 B.C. and then to Greece in the west by the soldiers of Alexander the Great after their Indian Campaign in the third century B.C.

EPIDEMIOLOGY

The prevalence of leprosy had declined since the introduction of World Health Organization-multi-drug therapy (WHO-MDT). This consists of dapsone 100 mg/day, rifampicin 600 mg/month, and clofazimine 300 mg/month and clofazimine 50 mg/day. This was first introduced in 1982. On a global basis, the number of registered cases fell from 5.4 million in 1985¹ to 0.88 million in 1997. The World Health Organization has set a target of eliminating leprosy as a public health problem (i.e. <1 case per 10,000 population) by the year

2000.² It is still highly prevalent in Central Africa, India, and South-East Asia. Eighty percent of cases are found in five countries (India, Brazil, Bangladesh, Indonesia and Myanmar).² There has been an increase in the age of onset with the peak incidence between 10-20 years and peak prevalence between 30-50 years of age. It is more common in males than females with a male to female ratio of 2:1. Studies indicate that individuals with HLA-DR2 are more prone to developing tuberculoid leprosy; while those with HLA-DQ1 develop lepromatous leprosy.³ In Orientals the prevalence of lepromatous leprosy is 30-40%, while in Africa 90% of cases are tuberculoid.⁴

In Hong Kong, the incidence of leprosy has declined due to improved housing, better health of the general population and improved treatment. The declining incidence of leprosy can be seen in table 1. From 1970 to 1997, 45% of new leprosy cases were tuberculoid; 30% were borderline, and 25% were lepromatous leprosy (Figure 1).

CLINICAL FEATURES

Leprosy is divided into paucibacillary and multibacillary types, depending on whether *M. leprae* are found on skin smear. Smear positive cases are classified as multibacillary leprosy and smear negative cases as paucibacillary leprosy. Leprosy is further divided into indeterminate leprosy, tuberculoid leprosy, borderline leprosy, lepromatous leprosy, primary neuritic leprosy.

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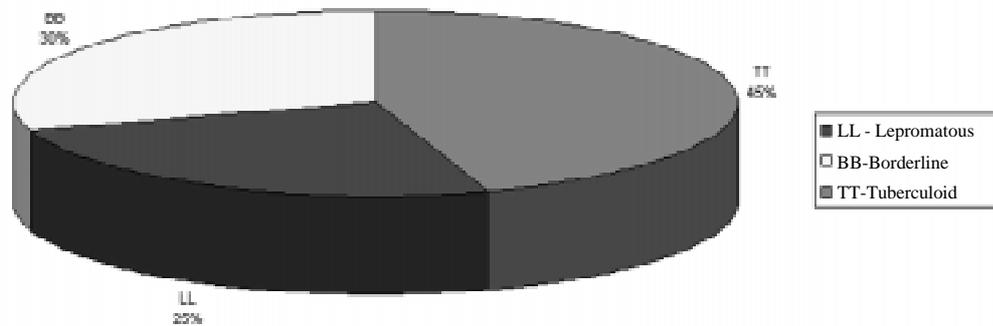


Figure 1: Subtypes of leprosy in Hong Kong

Table 1. Incidence of leprosy 1954-1997

Year	Number of new cases	Incidence per 100,000 population
1954	302	13.5
1959	297	10.0
1964	271	7.7
1969	125	3.55
1974	110	2.8
1979	69	1.4
1984	32	0.6
1989	26	0.4
1994	21	0.34
1997	11	0.16

Indeterminate leprosy

This represents the early phase of leprosy. It is from this form that the other types of leprosy develop, depending on the host immunity. It presents as a single or multiple asymmetrical, ill-defined macules and may be difficult to diagnose. Sensation may be normal or impaired, while hair growth and sweating are unaffected. Indeterminate leprosy may resolve spontaneously or progress. Skin smear is usually negative, although acid-fast bacilli may be found in the nerve endings.

Tuberculoid leprosy

This is the form associated with good host cell-mediated immunity. There is usually a single lesion although occasionally two or three lesions may be found. Hypopigmentation is due to the reduced number of melanocytes. Sensation is markedly impaired in the lesions, typically with loss of pain and/or touch and temperature. The other typical feature is enlarged nerves.

This often affects the radial, ulnar, posterior tibial nerve, and the lateral popliteal nerve. In general, any nerve near the lesion may be affected. The affected nerve may undergo caseation and liquefactive necrosis resulting in a cold abscess. Skin smear is usually negative while the lepromin test is positive, indicating good cell-mediated immunity.

Borderline leprosy

This is an unstable form of leprosy which may proceed to the tuberculoid or lepromatous pole, resulting in lepra reactions. It is further subdivided into borderline-tuberculoid (BT), mid-borderline (BB), and borderline-lepromatous (BL) leprosy. Erythematous, infiltrated patches with raised edges and depressed centres are characteristic. Annular lesions in leprosy are usually due to the borderline type. Lesions tend to be more numerous and less well-defined near the lepromatous pole, while fewer, more anaesthetic and well-defined near the tuberculoid end. Hypoaesthesia and reduced hair-growth are typical features of borderline type. Bacilli vary from being very few near the tuberculoid end to being numerous at the lepromatous end of the spectrum.

Lepromatous leprosy

Most cases of lepromatous leprosy have evolved from borderline leprosy as a result of downgrading reactions. Due to poor cell-mediated immunity, rapidly multiplying bacilli are found throughout the patient, being present in lacrimal secretions, nasal secretions, breast milk, blood, semen and faeces. There are numerous erythematous, ill-defined, infiltrated macules, papules and nodules resulting in leonine facies at advanced stages. There are often loss of the eyebrows, saddle nose deformity and ulceration of the nasal mucosa. Anaesthesia is not prominent in the initial stage.

However, the nerves gradually become fibrosed, resulting in extensive anaesthesia, claw hand and foot-drop. The eyes and testes are also affected, resulting in blindness and sterility. Lepromatous leprosy can be divided into an early subpolar phase (LLs) where lesions are macular; an infiltrated phase where the infiltrated skin is thickened and lesions are generalized with minimal sensory loss; and finally the polar phase (LLp) or nodular phase where generalized aggregation of the lesions occur. In this phase there is anergy for *M. leprae*, enabling rapid multiplication of bacilli. Nevertheless, not all patients pass through these phases. There may be few lesions but the skin smear is usually positive in untreated cases.

Primary neuritic leprosy

There is no cutaneous lesion in this form of leprosy. Sensory changes such as heaviness or tingling occur, due to the asymmetrical involvement of the peripheral nerve trunks. The ulnar nerve is most often affected. Frequently, these changes are due to underlying tuberculoid or borderline leprosy. Motor changes occur later, with deep reflexes retained until advanced disease. Light touch and temperature are lost sooner than pain and pressure. On the other hand, the nerves are tender in reactional states.

Neuritic leprosy is difficult to diagnose, as the skin lesions are not present and skin smear is negative. Nerve conduction studies and electromyography (EMG) support the diagnosis but often nerve biopsy is required for confirmation.

OTHER FORMS OF LEPROSY

Lucio phenomenon

This is a form of lepromatous leprosy where there is a total loss of host immunity. It is rare outside Mexico and Central America. There is diffuse infiltration of the skin with sensory loss, and skin smears are heavily positive. The Lucio phenomenon is characterised by painful lesions which become necrotic and ulcerated and occurs only in untreated patients.

Histoid leprosy

In this form, firm, erythematous, nodules appear on the chin, antecubital fossa, and the surface of the eye. These are often associated with relapse due to dapsone resistance. These nodules are found in the dermis and subdermis. In the skin biopsy, there are spindle-shaped histiocytes containing bacilli showing a whorled arrangement.

HISTOLOGY

Indeterminate leprosy

In this early stage, the picture is vague with no abnormality in the epidermis. Clusters of mononuclear cells are found in the dermis near blood vessels, nerves and appendages. A few bacilli may be seen near dermal nerve fibrils.

Tuberculoid leprosy

There are tuberculoid granulomas consisting of epithelioid cells, giant cells and lymphocytes in the dermis which may extend to the epidermis. There is infiltration of the cutaneous nerves, with occasional caseation necrosis. No bacillus is seen.

Borderline leprosy

A granuloma-free subepidermal zone with few bacilli is found in all types of borderline leprosy. Granulomas are well-defined in BT leprosy and become less distinct towards the lepromatous end, with the appearance of foamy macrophages in BL leprosy. Lymphocytes become fewer in number towards the lepromatous end.

Lepromatous leprosy

There is thinning of the epidermis with a diffuse, highly bacilliferous granuloma (leproma) in the dermis. This is formed by macrophages which have not differentiated into epithelioid cells and later have undergone fatty change to foamy cells. The neural cells show perineural inflammation initially, with gradual development of fibrosis in advanced stages.

LEPROMIN TEST

This measures the cell-mediated immunity (CMI). Autoclaved *M. leprae* are injected intradermally into the forearm, the result is read 48-72 hours (Fernandez reaction) and 3-4 weeks (Mitsuda reaction) later. The Fernandez reaction indicates the degree of delayed-type hypersensitivity (DTH) and the Mitsuda reaction indicates CMI. The Mitsuda reaction is not diagnostic as it is positive in normal individuals not exposed to *M. leprae* and negative in lepromatous leprosy.

RELAPSE IN LEPROSY

The dapsone resistance epidemic in the late 1970s led to a rise in the incidence of leprosy and to a search

for multi-drug regimens. Patients were kept on dapsone, with the recommended duration gradually increased from 5 years after smear negativity for lepromatous patients in the 1960s, to lifelong in the 1980s. This resulted in poor compliance and a high default rate. In addition, in order to reduce the number of lepra reactions, the dose of dapsone was gradually increased from a low-dose (25-50 mg/day) and maintained on 300-600 mg /week. In many cases, low-dose dapsone was used for long periods. These two factors probably led to the appearance of dapsone resistance and high incidence of relapse in the 1970s. Full-dose dapsone (700 mg/week) was recommended after the emergence of dapsone resistance. This led to a significant decrease in the incidence of secondary dapsone resistance (development of dapsone resistance during treatment with dapsone monotherapy).⁷ However, by the late 1970s full-dose dapsone was no longer effective in controlling leprosy. This led to the search for multi-drug therapy for leprosy. Studies have reported that the rate of relapse is significantly lower after the first four years following release from dapsone.⁶

The relapse rates after release from dapsone have varied from < 1% to 17%^{8,9} for tuberculoid leprosy and from 2% to 30% for lepromatous leprosy.^{10,11} Factors affecting relapse after dapsone include: a) poor compliance, b) low-dose dapsone, c) dapsone resistance, d) persistent *M. leprae*. In one study, skin biopsies were taken from leprosy lesions before treatment and at intervals up to 24 months later.¹² Small number (50,000-250,000 organisms) of persisting *M. leprae* were found in the skin biopsies even after treatment with regimens containing high-dose rifampicin (rifampicin 600 mg/day). This finding did not vary with the dose or duration of treatment. However, there has been evidence to suggest that the risk of relapse may not be as high as previously suspected.¹¹ In another study, skin biopsies were taken from sites of resolved leprosy lesions. It was found that in 22 of the 40 lepromatous leprosy patients studied, lepromatous granulomas were present even after clinical cure and smear-negativity.¹³ No life bacilli were found in these granulomas. The presence of these granulomas would indicate an ongoing antigenic stimulus. The continuous immune activity will result in damage to neural tissue. Laminin-alpha 2 is the target. There is also a higher incidence of *M. leprae* in nerve as compared to that in the skin biopsies.¹⁴

The relapse rate has been much lower after WHO-MDT was introduced (<1% in WHO studies). Sixty-seven relapses were detected among 20 paucibacillary and 141 multibacillary cases at a follow-up of nine years. The cumulative risk of relapse was 0.77%.¹⁵ However, the relapse rate was 20% in a study by Jamet on 35 multibacillary patients at 72.7 (+/- 17.3) months post-

MDT,¹⁶ as compared to a relapse rate of 2.9% at 41.9 (+/-12.1) months in a previous study.¹⁷ He also showed that a high initial bacterial load was associated with a higher risk of relapse. Eighteen of the 35 patients had a bacterial index (BI) > 4.0, of which 7 (38.9%) relapsed, while none of the remaining patients with BI < 4.0 relapsed. Although the small sample size warrants caution, it can be seen that the relapse rate will increase with time and that initial encouraging results should be interpreted with caution. It is likely that the time to relapse with WHO-MDT will be even longer than with dapsone. Studies have also shown that the risk of relapse is significantly related to the regularity of treatment during the smear positive period.¹⁸ A regularity of over 75% in lepromatous leprosy patients was associated with a median delay of relapse of 6.6 years, whereas with < 75% regularity, the median delay was 4.4 years.

In Hong Kong, between 1970-1997 there have been 56 relapses (Figure 2). Twelve relapsed after dapsone monotherapy completed, 35 relapsed while on dapsone monotherapy, and nine after stopping WHO-MDT. The average time to relapse following dapsone monotherapy and WHO-MDT were 6.35 years (range: 11 months-12 years) and 2.5 years (range: 1-5 years) respectively. The apparently shorter interval to relapse after MDT is probably due to the shorter period of observation for WHO-MDT (WHO-MDT introduced in 1982) as compared to dapsone.

LEPRA REACTIONS

Lepra reactions are immunologically mediated and represent a transient upgrading or downgrading of immunity. In the Type 1 reaction (reversal reaction) there is swelling of existing lesions which may be present initially or during treatment. This is due to a Type 1 T-helper cell response (Th1 response). Antigen is presented by macrophages which stimulate Th1 cells to produce interleukins (IL). Interleukin-1b, TNF-a and γ IFN are produced. This results in an upgrading of cell-mediated immunity.

Conversely with Type 2 lepra reactions (erythema nodosum leprosum), antigen presentation by B-lymphocytes stimulates a Type 2 T-helper cell response (Th 2 response) with increased production of IL-6, IL-8, IL-10 and antibody production, leading to induction of humoral immunity. IL-10 will also suppress the Th 1 response. Clinically, there are crops of tender subcutaneous nodules. These two cytokine profiles are known as the Th1/2 dichotomy. The Th 2 cytokine profile results in anergy to *M. leprae* whereas a Th 1 response is associated with good CMI and tuberculoid leprosy.¹⁹

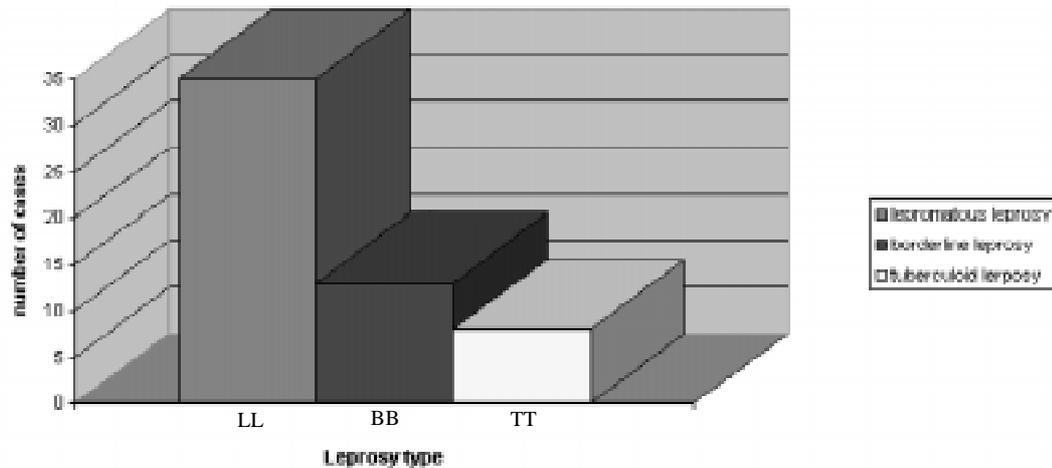


Figure 2: Relapse of leprosy in Hong Kong (1970-1997)

NEW TREATMENTS IN LEPROSY

Current WHO-MDT consists of six months dapsone 100 mg/day, rifampicin 600 mg/month (supervised) for paucibacillary patients. For multibacillary patients, dapsone 100 mg/day, rifampicin 600 mg/month (supervised) and clofazimine 300 mg/week (partly supervised) clofazimine 50 mg/day (unsupervised) is given for two years or until smear-negativity. In Hong Kong, multibacillary patients are kept on dapsone maintenance therapy after completion of WHO-MDT. This regimen has been effective but there have been occasions where therapy was not tolerated. In addition, there have been reports of rifampicin resistance when it has been used as monotherapy.

Ofloxacin, minocycline, sparflaxacin and clarithromycin have been reported to be effective against leprosy. They have been recommended as part of a multi-drug regimen to avoid resistance. Due to the economic burden of MDT, there have been attempts to shorten the duration of treatment. There has been an encouraging report of a single-dose regimen consisting of rifampicin 600 mg, ofloxacin 400 mg and minocycline 100 mg for single lesion paucibacillary leprosy.²⁰ However, as the follow-up period was only 18 months in this study, the result is to be interpreted with caution.

In addition, repeated BCG vaccination has also been shown to exert a protective effect against leprosy.²¹ One dose of BCG vaccination conferred 55% protection. This increased to 68% with two doses and 87% with three doses. This effect is due the cross-immunity as both *M. tuberculosis* and *M. leprae* share a common antigen, which is heat-shock protein 65.

CONCLUSION

The clinical picture of leprosy is affected by the host cell-mediated immunity. Current therapies are able to clear *M. leprae* effectively but small numbers of persisting organisms remain after therapy. The remaining bacterial load will be much smaller as compared to dapsone monotherapy and theoretically the time to relapse after current MDT will be longer. Long-term surveillance is therefore indicated.

Learning points:

Leprosy should be considered in any anaesthetic lesion or rash without an epidermal element. Persisters organisms can be found in clinically cured patients, therefore continual surveillance is required.

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Answers to Dermato-venereological Quiz on page 93

Answer (Question 1)

1. Pityriasis rubra pilaris (PRP) type 1.
The distinguishing features of PRP include "islands" of spared skin within generalized erythroderma, follicular keratotic papules, an orange hue to the involved skin, and palmoplantar keratoderma.
2. Psoriasiform dermatitis covered by alternating orthokeratosis and parakeratosis in both vertical and horizontal directions.
3. Complete remission will occur in 80% of patients within 3 years. Topical therapies include emollient, corticosteroid, keratolytic and calcipotriol. Retinoid is the first line systemic therapy. Other treatment modalities include: methotrexate, azathioprine, and phototherapy.

Answer (Question 2)

1. Autologous epidermal transplantation for vitiligo. Depigmented skin can also be seen adjacent to the OT towel. Suction blister is being prepared on the recipient site over the neck. Epidermal graft is obtained from the inner arm or lower abdomen similarly by suction and then transplanted to the recipient site.
2. a) Pigmentary change over the graft site. This will resolve with time.
b) Possible Koebner's phenomenon over graft site.
c) Skin infection.
3. Correct and accurate transplantation of the graft (which is thin and curls easily), post-operative graft immobilization and prevention of infection are important.