Chapter

Leprosy in the Modern Era

Syed Manzoor Kadri, Marija Petkovic, Arshi Taj and Ailbhe H. Brady

Abstract

Leprosy is a chronic infective disease that originates from the presence of pathogen agent *Mycobacterium leprae*. *Mycobacterium leprae* was discovered by the Norwegian doctor Gerhard Henrik Armauer Hansen in 1873. For the zoonotic transmission of M. leprae in the US the responsible insects are armadillos (*Dasypus novemcinctus*). M. leprae is an intracellular microorganism leading to loss of sensibility, innervation, intraepidermal impairment and lesions due to the absence of myelin in Schwann cells. *Mycobacterium leprae* has high infectivity and low pathogenicity. Incubation period is from 2 to 7 years. Leprosy is an infectious neurodegenerative disorder of the peripheral nervous system. Leprosy is the major cause of human disability due to neurological damage. Leprosy still represents one of the major causes of disabilities in humans. The most common complications are muscle weakness leading to atrophy, bone loss, amputations and blindness. In the case of chronic cutaneous hyperalgesia, there is a local increase in NGF levels. The application of anti-NGF antibodies may be of benefit in treating hyperalgesia in patients with neuropathy and impaired nerve endings. If combined, NGF, NT-3 and glial cell-line derived neurotrophic factor may be sustainable. In over 90% of human individuals an overall genetic resistance has been noted.

Keywords: *Mycobacterium leprae*, diagnosis, epidemiology, treatment, adult, children

1. Introduction

Leprosy is a chronic infective disease that originates from the presence of pathogen agent *Mycobacterium leprae*. *Mycobacterium leprae* was discovered by the Norwegian doctor Gerhard Henrik Armauer Hansen (**Figure 1**) in 1873 as the first proof that a person's disease is caused by bacteria [1].

For the zoonotic transmission of M. leprae in the US the responsible insects are armadillos (*Dasypus novemcinctus*).

Since ancient times, leprosy has been considered as one of the first major human epidemic diseases.

The first noted leprosy epidemic was in Europe in 1873 due to the detection of *Mycobacterium leprae* in Norway (Bergen).

These regions included the Iberian Peninsula, Sicily, the Balkans, southern Romania, the Baltics, and Scandinavia. In Norway in particular, scientists investigated the disease known as "Spedalsked", the Norwegian name for leprosy [1].

In 2015, the number of newly diagnosed cases of leprosy was 210,758 worldwide (**Figure 2**).

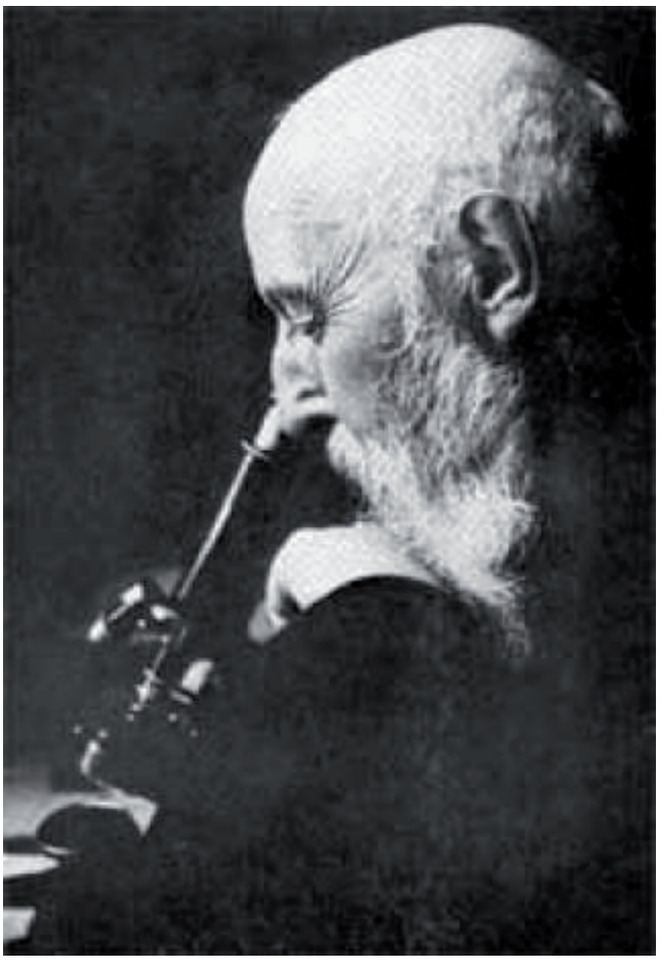

Figure 1.
Gerhard Henrik Armauer Hansen.

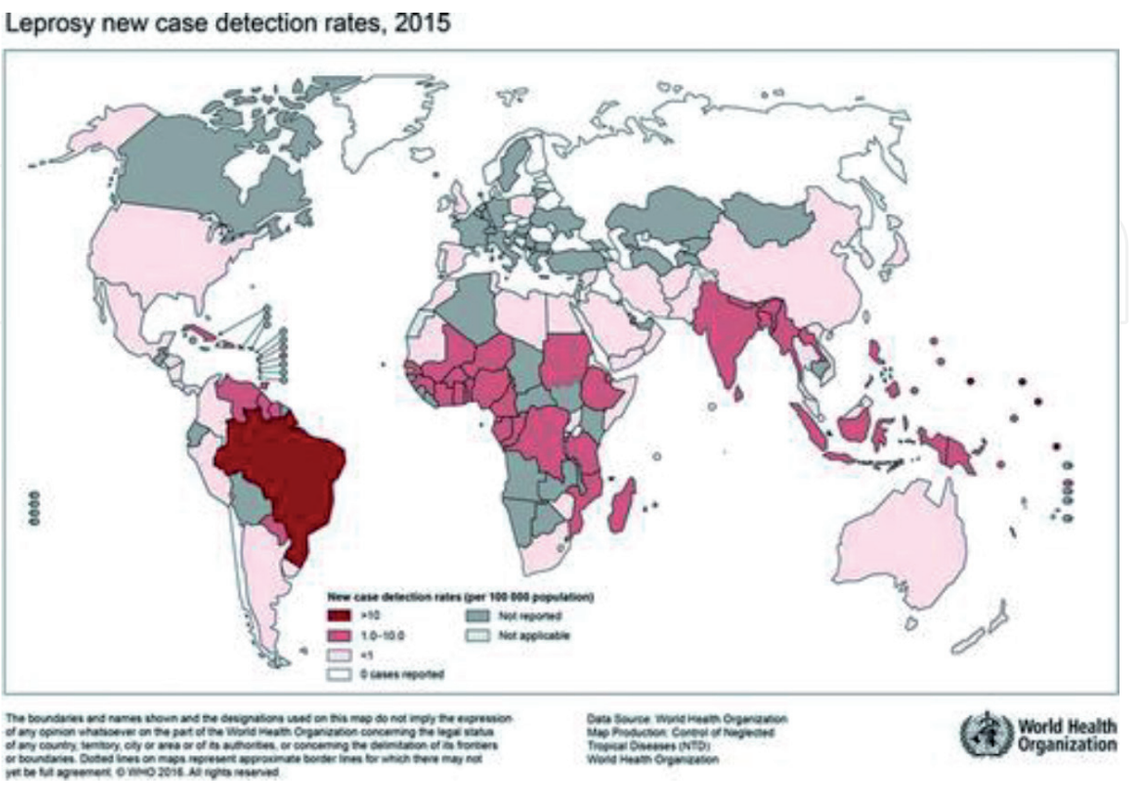

Figure 2.
Newly diagnosed cases of leprosy worldwide [2].

Transmission of leprosy persists despite efforts made by the World Health Organization (WHO). With the highest incidence in India, Brazil and Indonesia.

Mycobacterium leprae is a non-motile, acid-fast pathogen and cannot be cultured on any known medium. The most common route of transmission in humans may be via nasal droplets. Predisposing factor may be a prolonged contact with an infected individual with a high-bacterial load.

Leprosy still represents one of the major causes of disabilities in humans. It has been estimated that approximately 3 million individuals are affected.

Based on 193, 118 cases at the end of 2017, prevalence rate corresponds to 0.3/10,000.

2. History and epidemiology

M. leprae is an intracellular microorganism and an acid-resistant bacilli leading to a loss of sensibility, innervation, intraepidermal impairment and lesions due to the absence of myelin in Schwann cells. If the bacilli are numerous, they can be grouped in parallel or arranged in parallel.

M. leprae has high infectivity and low pathogenicity. The incubation period is from 2 to 7 years.

An individual is infected by inhalation of infectious aerosol or through the skin while contacting with nasal secretions and/or skin changes of the infected individual.

Children are more susceptible to leprosy than adults. Due to the slow proliferation of leprosy (the time of one generation is 14 days), the incubation period of the disease is quite prolonged (2–5 years).

Due to infiltration of the peripheral nerves, neuritis, anesthesia, trophic ulcerations, muscle atrophy and bone resorption occur.

3. Basic scientific considerations and pathology

Leprosy is an infectious neurodegenerative disorder of the peripheral nervous system. Thus, leprosy is the major cause of human disability due to neurological damage.

To this date, M. leprae has not been cultivated on artificial nutrients.

Nerve injury-associated tissue damage is the most prominent clinical consequence of leprosy.

In the process of leprosy-associated neuropathy, the presence of bacilli in nerve endings and Schwann cells induces a response mediated by macrophages and other cells that eventually leads to the appearance of immune-mediated lesions.

The most important cytokines are TNF-α, IL-6, IL-17 that are involved in the progression of neural lesions (**Figure 3**).

According to Antunes et al., it was concluded that in the individuals with neuritic leprosy, NGF-R immunoexpression was lower (nerve fiber, Schwann cells) than in control group (normal individuals). In the leprosy group, hypoesthesia was associated with decreased expression of NGF-R and PGP (protein gene product) 9.5.

TrkA receptors are detected in subepidermal fibers. TrkA receptor messenger RNA is produced in the skin. NGF are also present in keratinocytes and are in correlation with deficient thermal sensation [3].

NGF levels are depleted in nerve and skin lesions in leprosy the loss of NGF-dependent nociceptive fibers in damaged skin. An additional cause of decreased NGF is an impaired interaction between keratinocytes and nerves in affected skin.

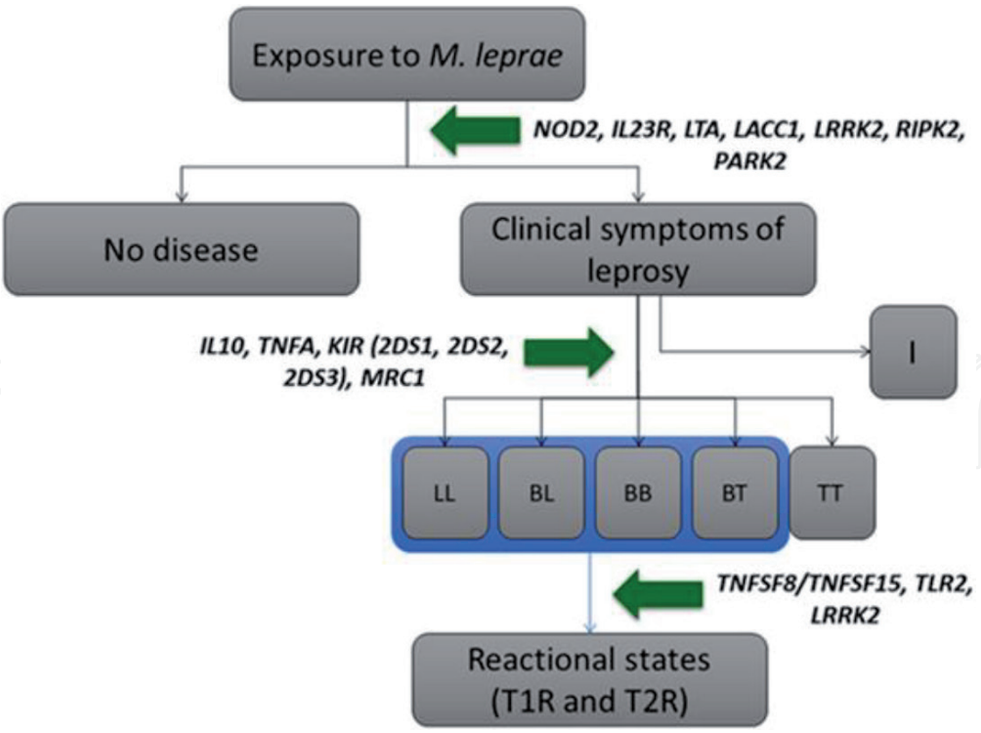

Figure 3.
Pathogenesis of leprosy [4].

Higher levels of NGF are observed in the lepromatous forms, while lower NGF levels are present in tuberculoid forms.

High levels of NGF are associated with lepromatous and decreased levels are associated with tuberculoid forms [5].

4. Classification of leprosy

Classification of leprosy according to immunity by Ridley and Jopling (**Figure 4**) consists of a 5 group-system based upon the clinical, histopathological, immunological and bacilloscopic factors:

1. Borderline-tuberculoid

2. Borderline-lepromatous

3. Borderline-borderline

4. Tuberculoid

   - Granulomatous lesions

   - Th1 (cell-mediated) immune chapter

5. Lepromatous

   - Th2 (an anti-inflammatory cytokine) characteristics

   - Multiplication of pathogen in macrophage phagosomes.

WHO	Ridley-Jopling	ICD-10	MeSH
Paucibacillary	tuberculoid ("TT"), borderline tuberculoid ("BT")	A30.1, A30.2	Tuberculoid
Multibacillary	midborderline or borderline ("BB")	A30.3	Borderline
Multibacillary	borderline lepromatous ("BL"), and lepromatous ("LL")	A30.4, A30.5	Lepromatous

Figure 4.
Leprosy classification.

WHO classification [6] according to the number of lesions consists of three groups:

1. Paucibacillary single-lesion leprosy (single skin lesion)

2. Paucibacillary leprosy (2–5 skin lesions)

3. Multibacillary leprosy (more than 5 skin lesions)

5. Clinical and laboratory diagnosis

Leprosy is transmitted via close and prolonged contact amongst healthy individuals and a bacillus-infected patient through inhalation of the bacilli contained in nasal secretions or Flügge droplets. The main route of transmission is the nasal mucosa. Leprosy, similar to other infectious diseases is a consequence of pathogen invasion of the host organism and transposition of the immunological barrier [7].

Transmission can occur by skin erosions, blood, vertical transmission, breast milk, and insect bites.

In infected individuals, there is a transitional period of nasal release of bacilli. The presence of specific DNA sequences of M. leprae in swabs or nasal biopsies and seropositivity suggest the carrier plays a role in the transmission of leprosy.

In the individuals with the solid immune system, leprosy is presented in tuberculoid form (solitary papules and plaques). Such skin changes may form erythematous plaques with raised borders and an annular appearance.

In the case of a defected immune system, lepromatous leprosy is presented with an impaired T-cell immunity leading to anergy. Clinically, this manifestation is shown as multiple red-brown-nodular infiltrate (lepromas) in the skin and mucous membranes.

"Leonine facies" is defined as the symmetrical centrofacial presentation of the cushion-like lesions, loss of the eyelashes and eyebrows [7].

Involvement of the nasal mucosa leads to destruction of the septum and deformity of the nasal skeleton (saddle nose). Subsequently, this destructive inflammatory process may include the entire nasopharynx, clinically characterized by mucosal ulcerations of the palate and larynx.

Multiple, poorly demarcated, hypopigmented papules, nodules, and/or infiltrated plaques are the hallmark of this form.

In case of chronic cutaneous hyperalgesia, there is a local increase in NGF levels. The application of anti-NGF antibodies may be of benefit in treating hyperalgesia in patients with neuropathy and impaired nerve endings. If combined, NGF, NT-3 and glial cell-line derived neurotrophic factor may be sustainable [8].

NGF has a potential modulatory role in nociception.

NGF may restore pain sensitivity and prevent the ulcer formation caused by nociceptive loss. Anti-NGF treatment may be of benefit in patients with hyperalgesia.

Other cytokine imbalances may be described as the imbalance in the proNGF/NGF ratio, increased TNF-α and p75 neurotrophin [9].

The main targets of M. leprae are Schwann cells. In case of the onset of Schwann cells degradation, peripheral neuropathy is the most common consequence. It has been documented that NGF may act as a protective factor for Schwann cells. Thus, low levels of NGF directly are responsible for the development of neuropathy.

NGF are involved in the reparation of neuronal cells and induction of fibroblast migration. They exhibit proliferative and antiapoptotic effects on keratinocytes and endothelial cells [10].

The incidence of nerve impairment in the individuals with paucibacillary leprosy is present in 10% of cases, whilst in multibacillary leprosy in 40%.

TGF-β is involved in the tissue reparation processes due to its anti-inflammatory attributes.

Leprosy is diagnosed mainly on the basis of a clinical picture. For bacteriological diagnosis, a nose swab, scraping or cutaneous skin changes are taken.

The diagnosis is based on the findings of acidoalcohol resistant bacteria in lepromatous leprosy and histopathological findings. Experimental animals (armadillo, mouse) are used to isolate M. leprae. Skin test with lepromine (Mitsuda test) is positive for tuberculoid leprosy. A positive lepromin test is linked to the ability to develop a granulomatous response [11].

A serological test method with good sensitivity in multibacillary forms (approximately 70%) involves the measurement of antibodies against a phenolic glycolipid (PGL-1; 35 kDa) in the bacterial cell wall.

It is recommended to perform skin biopsies taken from the margins of the lesions and should also include subcutaneous tissue.

Bacterial index (BI): scale for assessing the number of leprosy bacteria in skin smears may be according to the bacterial count per visual field(s)	
a. 1–10/100	1 +
b. 1–10/10	2 +
c. 1–10/1	3 +
d. 10–100/1	4 +
e. 100–1000/1	5 +
f. > 1000/1	6 +

In certain individuals, pseudoabscesses along nerves and nerve thickening may be present.

Thickened nerves may be detected by palpation along the course of the supraorbital, retroauricular, ulnar, median, superficial radial, common peroneal, superficial peroneal, posterior tibial, and sural nerves. The initial functional tests implicate weakness (paresis) or loss (paralysis) of muscle strength [12].

Thermosensitivity is checked using a heated test tube with a lighter. The test tube is then held to the patient's skin lesion and the corresponding skin. The test is performed placing a tube with water at room temperature to the skin lesions. The patient is then asked to detect the difference between hot and cold [13].

The neurological examination conducted by a specialist includes EMG, nerve ultrasound, and magnetic resonance imaging. Nerve biopsies are preferably taken from thickened superficial and thus readily accessible nerves such as the sural nerve, the superficial peroneal nerve, the ulnar nerve, and the saphenous nerve.

6. Clinical presentation

The initial stage of leprosy is non-specific presenting with one or more hypopigmented macules.

There have been four noted immunologic leprosy reactions. Type 1 reaction represents a hypersensitivity reaction to M. leprae antigens clinically characterized by sudden onset of urticarial swelling of the leprous skin lesions. It may also be associated with acute and very painful neuritides with loss of sensory and motor function.

Pathophysiologically, type 2 reaction (Syn. erythema nodosum leprosum) is characterized by the occurrence of painful violaceous- erythematous cutaneous or subcutaneous nodules. Type 3 reaction (Syn. Lucio's phenomenon).

Myalgia, arthralgia, and osseous pain are symptoms associated with a type 2 reaction [13].

The first leprosy classification by WHO was applied in 1966 based upon the histological picture – the Ridely-Jopling classification. It shows two forms of leprosy – its mild and severe defect of cell-mediated immunity: tuberculoid (paucibacillary) and lepromatous (multibacillary) leprosy with the following subgroups: borderline tuberculoid (BT), borderline lepromatous (BL) and borderline lepromatous leprosy (BL) [14]. This classification is detailed earlier in the chapter.

7. Complications

The most common complications are muscle weakness leading to atrophy, bone loss, amputations and blindness.

In the case of chronic cutaneous hyperalgesia, there is a local increase in NGF levels. The application of anti-NGF antibodies may be of benefit in treating hyperalgesia in patients with neuropathy and impaired nerve endings. If combined, NGF, NT-3 and glial cell-line derived neurotrophic factor may be sustainable.

In over 90% of human individuals an overall genetic resistance has been noted.

8. Systemic involvement and special situations

Overall, leprosy is a granulomatous inflammatory process. It causes intraneural pressure induced atrophy, palpable nerve thickening and progressive loss of neural functions with necrosis.

Histologically, there is epi-, peri- and endoneural fibrosis.

The most commonly affected nerve structures are: n. ulnaris located in the ulnar groove, n. medianus in the vicinity of the carpal tunnel, *n. tibialis* posterior, superficial branch of the radial nerve, sural nerve posteriorly of the malleolus, great auricular nerve as well as facial nerve, frontal and cervical branches.

Clinically, the resultant ocular muscle paralysis causes lagophthalmos, subsequently facilitating secondary corneal infections due to incomplete lid closure (Bell's palsy).

Sensory loss of the ophthalmic branch (V1) of the trigeminal nerve, too, results in corneal anesthesia, thus facilitating bacterial corneal ulceration.

9. Therapeutics

In the individuals with type 1 leprosy reactions (reversal reaction), the systemic administration of corticosteroids (initial dose of 40–60 mg prednisolone for 14 days, than gradually increase by 5 mg every 14 days).

Type 2 reaction is treated with the administration of thalidomide (100–400 mg/per day) plus the administration of systemic corticosteroids most commonly prednisolone 40 mg for 5 days [13].

In the case of syn. Lucio's phenomenon (type 3 reaction) the use of systemic corticosteroids are the first choice (**Figure 5**).

In the patient with nerve damage, it is necessary to incorporate active and passive physical therapy, local skin care if acral mutilations are present. Certain individuals require orthopedic prosthesis as well as reconstructive procedure(s) (nose reconstruction, tarsorrhaphy, hand surgery, etc.) [13].

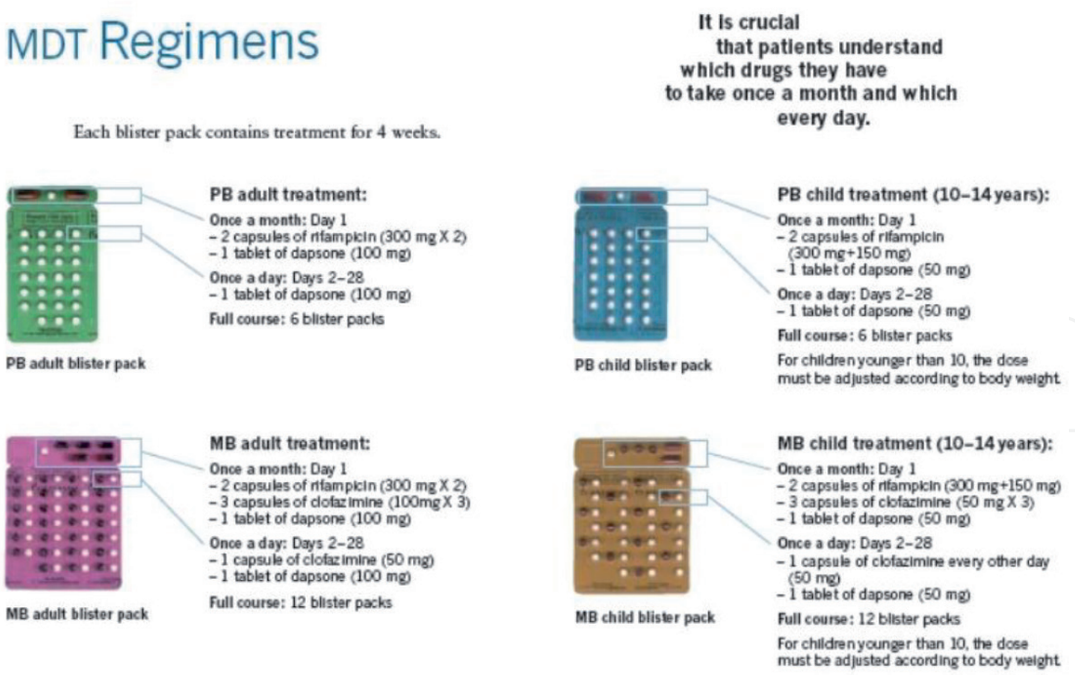

Figure 5.
Leprosy treatment modalities.

10. Prophylaxis and monitoring

The early diagnosis and treatment of leprosy are preventive measures in the initial spreading of this infectious disease. Hemoprophylaxis in children exposed

to infection is also required (BCG vaccine). For the treatment of leprosy, sulphonic preparations (dapsone) and rifampicin are used. The duration of treatment is prolonged – from 6 months to 2 years [15].

11. Miscellaneous issues

Recent studies suggested that the presence of the PARK2/PACRG gene (chromosome 6q25-q27) as well as the presence of the NRAMP1 gene (chromosome 2q35) is linked to the higher leprosy susceptibility.

TAP1 and TAP2 (transporter associated with antigen processing) genes (located on chromosome 6p21), TNF-α (tumor necrosis factor alpha) (chromosome 6p21), and the VDR (vitamin D receptor) gene (chromosome 12q12) are associated with the innate and adaptive immunity [15].

In the majority of infected individuals, leprosy takes on an intermediate form, which may – to a variable degree – show clinical features of tuberculoid and lepromatous leprosy. This intermediate form is referred to as borderline leprosy.

In PB forms it has been noted higher cellular response to M.leprae due to the Th1 cytokines such as IFN-y. There are also lower antibody titers to M. leprae – specific antigens. In the individuals with MB form of leprosy there is an absence of the capacity to mount a cell mediated response due to T cell anergy. There is a high antibody titer to M. leprae antigens (PGL-1) [16].

12. Rehabilitation and social issues and future prospects

In untreated individuals with leprosy, there are progressive, destructive and irreversible body impairments. Such deformities and ulcers are the consequence of the skin, muscle and nerve invasion.

Recent studies [15] suggest the role of PARK2 and *LACC1* as one of the major genetic factors involved in the pathogenesis of leprosy, thus implicating the necessity of further investigational studies.

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