Provisional chapter

An Update on the Epidemiology, Diagnosis and Treatment of Leprosy

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Additional information is available at the end of the chapter

Abstract

Leprosy is a granulomatous, chronic infection caused by *Mycobacterium leprae* that has been reported for than 2000 years. The infection primarily affects the skin and peripheral nerves. *M. leprae* is bacterium that cannot be cultured in vitro and transmission and pathophysiological data is still uncertain and limited. Today the prevalence of this ancient disease is declining in most around the world. This decline is a direct effect of widespread administration by public health workers of multidrug therapy. However, emerging despite the use of multidrug therapy, identifying and monitoring resistance are still necessary.

Keywords: leprosy, Hansen's disease, epidemiology, clinical findings, multidrug treatment

1. Introduction

Leprosy is an ancient, granulomatous and chronic infection that caused by *Mycobacterium leprae*. It primarily affects the skin and peripheral nerves and late diagnosis of the leprosy related with the various complications and disabilities. Clinical findings of leprosy based on the cellular immune response of the patient and the duration of the disease.

Diagnosis is made by clinical examination; however, it must be supported with laboratory to determine the classification and the treatment of the disease.

In leprosy, Multi Drug Therapy (MDT) has been recommended since 1982 as the standard treatment. With MDT, relapse and the number of the new leprosy cases decreased. However, it is still important and necessary to closely monitorize the patients to prevent and eliminate the leprosy.

2. Epidemiology

According to data from the World Health Organization (WHO), there are 5.35 million leprosy patients in 1985, and this figure has declined to 210,758 in 2015 [1, 2]. The most probable cause of this decline in prevalence is the increasing public awareness, trainings made regarding diagnosis and treatment after the worldwide determination of leprosy as a public health problem [3]. When the prevalence of leprosy is determined, the data of registered patients receiving MDT every year are used. While the state of the disease on the world is determined, aside from prevalence, new patient detection rates and grade-2 disabilities (G2D) definitions and new cases with visible deformities are also used by WHO [2].

In reducing of the prevalence of leprosy over a period of several years, in particular, reducing the treatment with dapsone for many years (4–10) to up to 1 year with MDT was effective [4, 5]. In contrast with the decline in prevalence, the new patient detection rate continued to increase until 2001. After 2001, the number of new diagnoses in parallel with the decrease in prevalence due to the early diagnosis and the success of MDT has decreased [5]. The healthcare infrastructure, which plays a very important role in detecting and controlling the disease, and the accessibility of health services directly affect these rates [6].

At the end of 2015, the prevalence was calculated to be 0.29 (174,608 cases) per 100,000 population, and the rate of new cases was calculated to be 3.2 (210,758 cases) per 100,000 population, according to the number of patients receiving MDT in collected data by WHO from 138 countries [2]. Although the programs against leprosy are being prepared worldwide, currently, 14 countries, each reporting more than 1000 new patients per year, are generating 95% of newly diagnosed patients worldwide. In 2015, India alone accounts for 60% (127,326) of newly diagnosed patients, 13% of Brazil (26,395) and 8% of Indonesia. The Democratic Republic of the Congo, Ethiopia, Madagascar, Mozambique, Nigeria, the United Republic of Tanzania, Bangladesh, Nepal, Sri Lanka, Myanmar and Philippines totally have a new patient detection rate of 14%. Although the rates vary in different countries, on average, 38.8% of the patients reported worldwide are woman and 8.9% of them are children. It is rare to have leprosy in infancy due to long incubation period [7].

The rate of G2D, which indicates identification of early signs and symptoms of leprosy and the response to treatment, is around 6.7% worldwide (1409 cases), indicating a delay in the detection of cases where this rate is still high [2]. The aim of the Global leprosy 2016–2020 is to reduce G2D ratio to less than 1 per 1 billion worldwide; and to withdraw the G2D ratio to zero in children [8].

2.1. Contamination

Despite the fact that leprosy is a very old disease, we still have a limited knowledge of contamination routes and reservoirs. Contamination usually occurs after prolonged contact with the nasal and oral secretions of lepromatous leprosy (LL) patients infected and untreated with *M. leprae* [9]. However, many cases have been reported supporting the possibility of transmission by different ways, and discussions on different ways of transmission are continuing. There are reports that leprosy cases reported to develop by tattooing and accidental needle penetration support that they can be transmitted through damaged skin, there are also reports supporting undamaged

skin contamination [10–13]. In addition, leprosy cases seen in the infant period also suggest a possible infection from mother via blood or with breast milk [7, 14, 15]. Numerous cases of leprosy following direct or indirect contact, especially with nine-band armadillo, have been reported [16, 17]. In addition, a leprosy case developed after blood transfusion has been reported [18].

Bacillus *M. leprae* is showed by methods, e.g., skin biopsy, direct skin smear and electron microscopy; in different ratios in saliva, oral mucosa, hair follicle, hair shaft, sweat gland and canal, in the sebaceous gland orifice, in the mother's milk, and very little in the placenta [13, 15, 19–24]. It should be kept in mind that leprosy, which still continues to be a public health problem, may have different modes of transmission.

2.2. Reservoir

Although *M. leprae* is thought to be a largely human-depended parasite for a very long time, there is so much evidence supporting a reservoir other than human [25]. According to recent data, there is no significant decrease in new case detection rates between 2010 and 2015, suggesting that there may be reservoirs other than human [2]. The development of leprosy cases after direct or indirect contact with the nine-banded armodillo in the United States of America (USA) supports this idea [16, 17, 26]. In female chimpanzees brought from Africa to Japan for clinical trial purposes, development of leprosy after 30 years is important for the evidence regarding that leprosy may have both an incubation period and a non-human reservoir [27]. Findings also show that *M. leprae* is also present in environments such as insects, amoebae, soil, and water [25, 28–31]. Considering that bacillus can survive for 46 days in moist environment and 60 days in water; even backwater may become the medium in which they can survive for a long time [32].

2.3. Incubation

Since there is no serological or biological method that may detect *M. leprae* in the latent phase, which is subclinic, it is not yet possible to identify exactly the duration of the incubation; but observational estimates can be made. The estimated average incubation period for multibacillary leprosy (MB) is 5–10 years and sometimes more; for paucibacillary leprosy (PB), the average incubation period is 2–5 years [5].

2.4. Risk factors

2.4.1. Contact

In a case control study, when compared to the control group, those who had social contact and when compared to living in the same aquifer, those who are core households have a higher risk [33, 34].

2.4.2. Age

According to many specialist age is a risk factor and children below 14 years old who is in contact with MB patients as a householder are found to be at greater risk than adults [35–37].

In addition, a study showing that bimodal distribution of risk for age has been shown that the risk increase ages 5–15 years and over 30 years.

2.4.3. Gender

Although there are a number of studies showing no significant difference between men and women, there is also a study reported that men are at greater risk [34–36].

2.4.4. Leprosy type and physical distance to the patient

Compared to the general population, sharing the same house with a leprosy patient increases the risk. Contact with MB leprosy patients is more risky when compared to contact with patients with PB single lesion leprosy, while the risk of contact with MB patients is similar to contact with PB leprosy patients with 2–5 lesions [34, 36, 38]. If there are two or more patients in the same house, the risk of contamination doubles [11].

2.4.5. BCG vaccine

For individuals in contact with the general population and leprosy patients, BCG vaccination administration at repeated doses provides protection against the leprosy [39–41]. Those who live in the same household and do not vaccinated with BCG vaccine are at greater risk [42].

2.4.6. Genetic distance

Studies have been carried out for years to clarify whether there is a relationship between leprosy and genetics. Although not fully adequate, there are conclusions that support this idea. Moet et al. reported that genetic association is a risk factor predisposing to leprosy, regardless of physical distance [34]. Mire et al. found that the chromosome 6q25 locus was associated with leprosy susceptibility; Siddiqui et al. showed that the 10p13 locus was associated with PB leprosy [43]. There are also studies showing that HLA DR2 and non-HLA (SLC11A1, formerly NRAMP1 and TNF alpha) genes are also associated with leprosy [44, 45]. Genomic studies are important in combating leprosy in terms of having potential for improvement in treatment and vaccination. On the other hand, the presence of IL-17F (7488 t > C) single nucleotide polymorphism and the presence of IL-4 gene 4-590 T/C polymorphism are associated with decreased predisposition to leprosy [46, 47].

3. Microbiology and genetic

M. leprae is a compulsory intracellular organism, which is a fast-staining, very slow-growing (doubling time 14 days), which can reproduce at lower temperatures than body temperature [48]. Unlike other bacteria, it is thought that the reproduction pattern is not algorithmic. While the regions where it can reproduce in human body are at 25–33°C, whereas no *M. leprae* involvement is observed at 35–36°C regions [49].

Reproduction of *M. leprae* in vitro conditions has not been fully successful until now and the reason for this is still unclear. Amako et al. reached results showing that *M. leprae* Thai-53 strain grew in vitro in different media by digital droplet PCR method [50]. Most of the studies on the *M. leprae* have been carried out on armadillos. Low body temperatures (33–35°) of armadillos (*Dasypus novemcinctus*), long life cycles, and adequate body sizes have made them suitable hosts in experimental areas [26].

In 2001, by dissolving the genome sequence of *M. leprae*, new information about the disease has begun to be obtained [51]. *M. leprae* has the smallest genome among the mycobacteria species. *M. leprae* bacillus has undergone severe genomic disruption and diminution with reductive evolution [52]. Reductive evolution, especially in catabolism, has removed metabolic pathways along with control pathways [53]. More than half of the genome consists of pseudogenes, inactive reading frames or regulating sequences. In addition, dominance of the bacillus genome has led to advances in topics such as molecular epidemiology, drug-susceptibility testing, and understanding of the spread of the bacterium over the world [52].

4. Classification

Leprosy exhibits a broad spectrum of clinical and histopathological findings based on the cellular immune response of the host. In 1966, Ridley and Jopling classified leprosy according to clinical and histopathologic features [54, 55]. According to this classification system there is a tuberculous form (TT) consisting of a strong immune response and a small number of microorganisms at one end and a weak immunologic response and a lepromatous form (LL) overloading of microorganisms at the other end and three types of borderline leprosy; borderline tuberculoid leprosy (BT), mid-borderline (BB), borderline lepromatous leprosy (BL) between these two end. Conceptually, tuberculoid leprosy (TT) and lepromatous leprosy (LL) are clinically stable, while borderline forms may shift to stronger or weaker immunity.

In 1997, the WHO created a classification to provide leprosy treatment based on the number of lesions present, regardless of the size, localization, and histopathological features of the lesions, without laboratory support in endemic areas [56]. According to these, leprosy is divided to 3 subgroup: single lesion leprosy, PB, 2–5 lesions and MB, more than 5 lesions. According to the WHO classification, BT may be considered in the PB, BB and BL may be considered in the MB spectrum.

5. Clinics

Clinical findings of leprosy are primarily due to skin and nervous system involvement. There are five common types of peripheral nerve changes:

1. Enlargement of peripheral nerves: Peripheral nerves are more frequently affected by superficial placement. Unique findings such as anesthesia or hypoesthesia may develop as well as sensitivity and enlargement [55, 57]. Ulnar nerve in the elbow, median and superficial

radial cutaneous nerve in the wrist, large common auricular nerve in the neck, and common peroneal nerve enlargement in the popliteal fossa can be detected by palpation [57].

2. Presence of sensory defects such as anesthesia and hypoesthesia in skin lesions.
3. Sensory and motor function losses may occur depending on the location of nerves that are involved. General neurological examination was performed and neurological changes such as drop foot, flexion contracture 4–5 of the fingers, muscular atrophy, facial paralysis, and lagophthalmia may be detected [57].
4. Depending on the influence of thin, unmyelinated Type C fibers responsible for the transmission of senses such as light touch, pain, hot, and cold; the sensory loss in the glove-stocking pattern may be observed first in the hot-cold discrimination.
5. Anaphylaxis of palmoplantar area may be observed by the effected sympathetic nerve fibers.

Clinical forms of leprosy are determined according to clinical, bacteriological, immunological and histopathological criteria. According to that, leprosy has five clinical types:

5.1. Tuberculoid leprosy

It is a form of strong immune response that can be followed by spontaneous healing. Primary skin lesions are hairless, faintly elevated and endure, erythematous, squamous, annular plaques, which can be accompanied by neural involvements such as sharp anesthesia and hyperesthesia. The number of lesions is often solitary and does not exceed 10 cm in size. It can be seen as hypopigmented lesions in which partial pigment loss is observed, especially in dark-skinned individuals [54, 58]. Lesions should be examined thoroughly in terms of alopecia. Even if the enlargement and tenderness of the peripheral nerves near the cutaneous lesion are not detected, the lesion itself is typically hyperesthesia and anhidrotic [58].

5.2. Borderline tuberculoid leprosy

Although the immune response is sufficient to limit the disease, it is insufficient for spontaneous recovery [59]. Patients in this form may have a TT upgrade or borderline leprosy downgrade according to the change in the immunological response. Primary skin lesions are sharply defined, multiple, asymmetric, annular plaques and papules [54]. Lesions are less indurated and eleve, less erythematous, scarless, or slightly squamous than TT. The lesions can be seen in size to cover the entire limb. The lesions can be seen in size to cover the entire extremity. Loss of sense is observed in all lesions and nerve involvement (enlargement and paralysis) is usually asymmetry.

5.3. Mid-borderline leprosy

Immunologically, the two extremities are the midpoint of the spectrum [59]. The severity of cutaneous findings and neurological changes depend on which end of the patient is closer to. Primer skin lesions are generally asymmetric, alopecic, annular, sharply defined and broad platelets with the appearance of "Swiss cheese" where clinically normal skin islets are found.

5.4. Borderline lepromatous leprosy

The immune system is weak enough to stop bacterial proliferation but sufficient to suppress inflammation that causes tissue damage [59]. Clinical findings are considerably diverse. Lepromatous lepra-like weak-edged and tuberculoid lepra-like sharp-edged plaques providing a classical dimorphic annular appearance are seen in only one of three patients [54]. Large plaques with sharp or weak edges and normal papules and nodules on which normal skin islands are visible can also be observed. The number of lesions varies from solitary to multiple. While the annular plaque lesions show asymmetrical placement, the nodules localized symmetrically. Neurological involvement is common and severe sensorimotor damage can be observed.

5.5. Lepromatous leprosy

Extensive disease is seen due to the inadequate cellular immune response. Classical lesions are characterized by multiple, diffuse, often symmetric, sharply defined papules, plaques and nodules. Involvement areas are usually the face, the hip and the lower extremity (**Figure 1**). The infiltration of the forehead skin leads to generation of lion face, which is a characteristic facial appearance (**Figure 2**). Hair loss is widespread, especially in the eyebrows (madarosis) and lashes [60].

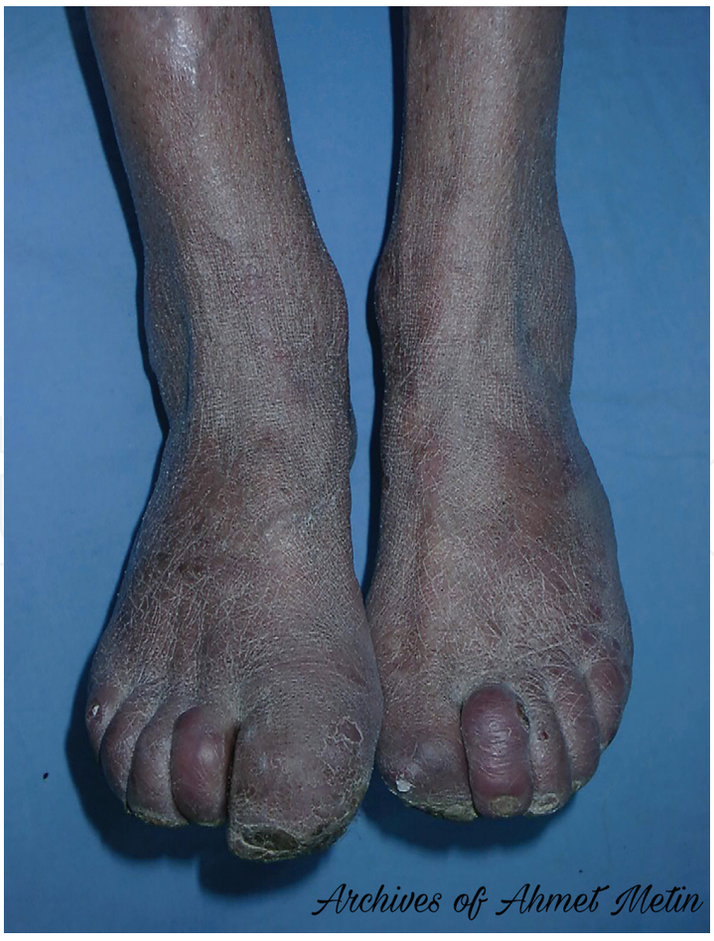

Figure 1. Lower extremity involvement.

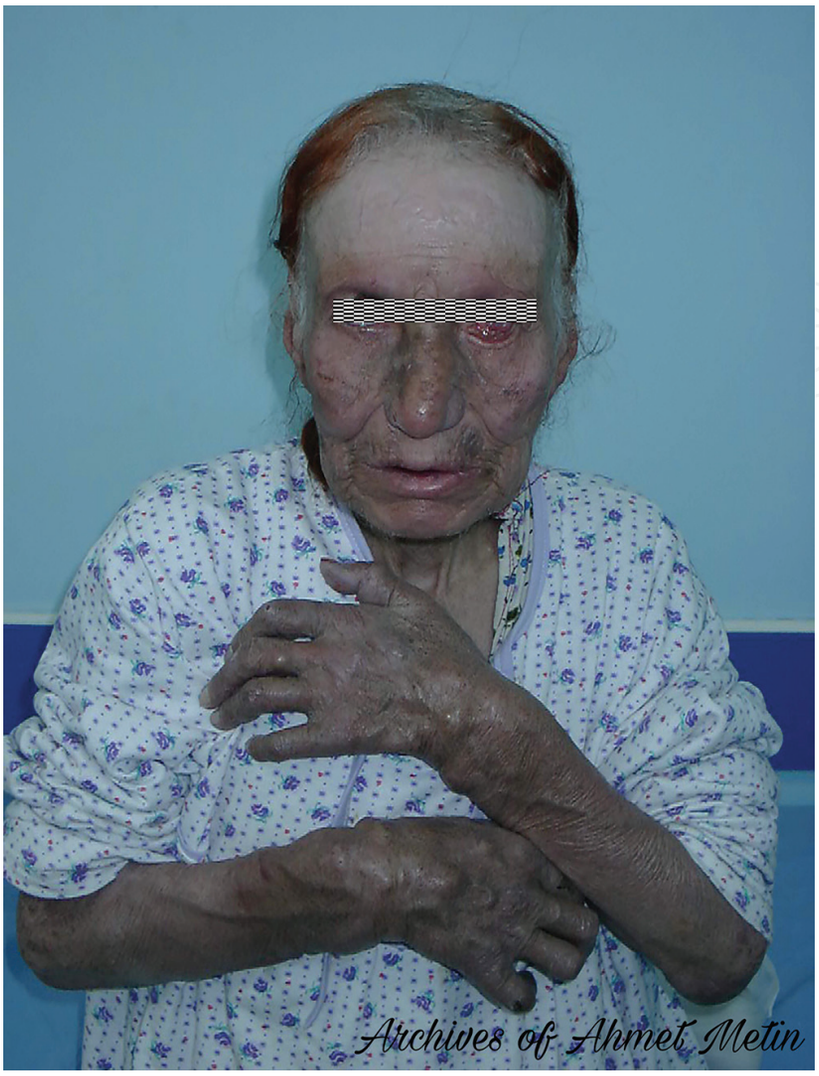

Figure 2. Characteristic facial appearance (lion face).

6. Complications

Corneal dryness, abrasion and ulceration are very common in patients with leprosy due to the secretory irregularity and corneal insensitivity. A careful eye examination should be performed in every leprosy patient to prevent serious complications that can result in blindness.

Depending on the perforation and collapse of the nasal septum, saddle nose and rhinitis-like findings can be observed. Snoring due to nodule occurrence in vocal cords and larynx involvement, and gynecomastia, impotence and infertility as a result of decrease in blood testosterone level due to testicular involvement in male patients may be seen [61].

Venous insufficiency due to endothelial involvement of the valves of deep venous vessels may lead to stasis dermatitis and venous ulcers.

In the advanced disease phase, multiorgan involvement (liver, spleen, peripheral lymph nodes, bone marrow) can be observed.

7. Immunologic reactions

Immunological reactions are inflammatory conditions that clinicians and patients may encounter before, during, or months or years after treatment [62]. Approximately 30–50% of patients are involved. There are two types of reactions that are linked to different immunological mechanisms that are not fully understood: Type 1 and type 2 [63]. These immunological reactions may mimic the drug reaction, the clinician should pay attention to that they are not drug reactions and that treatment should not be interrupted. In both types of reactions, general weakness, fatigue and fever can be observed. Other clinical findings differ according to the developing reaction.

Type 1 reaction: Typically occurs in TT and BT. It is due to an increase in cell-mediated immunity and a delayed-type hypersensitivity reaction to *M. leprae* antigens [55, 57, 63, 64]. Characteristic clinical findings are increased inflammation in existing lesions, formation of new lesions, pain and sensitivity in nerves (neuritis), progressive neurological failure.

Type 2 reaction: Typically, BL and LL patients develop when treatment begins. Pregnancy and pyogenic infections may induce. The type 2 reaction due to the formation of immune complex with hyper humoral immunity represents cutaneous and systemic small vessel vasculitis [55]. Characteristic clinical findings; painful nodular lesions (erythema nodosum leprosum) that occur suddenly, severe swelling and pain in the joints, iridocyclitis, orchitis, sensitive lymphadenopathy, glomerulonephritis, and hepatosplenomegaly [57, 63, 64].

Lucio phenomenon is a rare complication characterized by sudden-onset, necrotizing cutaneous small vessel vasculitis in diffuse, untreated LL patients in the Mexican and Caribbean region [65]. Lesions that are painful but have no increase in temperature can be cured by scarring. Ulceration especially may be observed in knees.

8. Differential diagnosis

Although reduction and absence of sensory perception distinguish leprosy lesions from other diseases, this finding may not always be detectable. With the reason that a wide variety of cutaneous lesions are present, leprosy can be confused with many diseases. In suspected patients, the exact diagnosis is made by skin biopsy.

Hypopigmented lesions may mimic pityriasis alba, pityriasis versicolor, mycosis fungoides and sarcoidosis [66].

Figured erythematous plaques may be confused with fungal infections, annular psoriasis, sarcoidosis, mycosis fungoides, lichen planus, systemic lupus erythematosus [66].

Infiltrated plaques and nodules generate definitive diagnosis with cutaneous leiomyoma, sarcoidosis, syphilis, keloid, cutaneous lymphoma, granuloma annulare [66].

In addition, definitive diagnosis of type 1 reaction includes acute lupus erythematosus, drug reactions, cellulitis; the definitive diagnosis of the type 2 reaction should be considered to include other conditions that may cause vasculitis and panniculitis.

9. Diagnosis

For diagnosis, leprosy must first come to mind. Although diagnosis is made substantially by clinic examination, diagnosis must be supported by laboratory for classification and treatment. Microbiological and pathological tests should be performed after history and clinical evaluation [67]. WHO recommends that individuals with one of the two cardinal findings in endemic regions are considered to be leprosy [68].

- Lesions compatible with leprosy with sensory loss (with or without nerve thickening).
- Positive skin smear.

Hypoesthesia skin lesion is the most important diagnostic factor because it is not expected in another skin disease other than leprosy. After evaluation of skin lesions, peripheral nerves should be palpated for thickening, and nerve examination of lesions and distal extremities should be performed [69]. Conjunctiva and corneal examination should also be made.

9.1. Sampling

Skin smear, a rapid diagnostic method, requires experience. The skin compressed between the thumb and index finger is cut with lancet with a width of 5 mm and a depth of 3 mm. The collected dermal fluid is spread on the lame. Tissue fluid should not be bloody. The most preferred regions are the earlobe, elbow and knee extensor faces. It may require three to six repetitions. The result is generally negative in less bacillar and TT. Nasal sampling is not recommended, especially because of fragility in LL cases. A 4 mm punch biopsy is the ideal method for sampling. The biopsy should be taken from the most erythematous, contagious and expanding area. Nerve biopsy may be required to support diagnosis, especially in cases of pure nerve involvement [67].

9.2. Microscopic examination

In vitro *M. leprae* culture is not possible. Demonstration of acid-resistant bacilli in material taken by skin smear or biopsy is standard diagnostic technique. With Ziehl-Neelsen staining, acid-resistant basils are colored fuchsia in blue background [67]. Bacteriological index (BI) is determined by rating between 1+ (1 bacteria in every 100 area) and 6+ (min. 1000 bacillus in every area) with the amount of bacteria in each microscope area. Patients with BI scores lower than 2 are considered as PB, whereas BI scores above 2 are considered MB [69].

9.2.1. Molecular methods

One of the molecular diagnostic methods, PCR, is the detection of *M. leprae* DNA. Biopsy material, tissue fluid, blood, urine, nerve tissue, oral and nasal mucosa swab and ocular lesions can be used for PCR [70]. While the specifity can be 100%, the sensitivity ranges from 34% to 80% in cases with PB forms to greater than 90% in cases with MB forms of the disease. The support of diagnosis is an important diagnostic tool in treatment follow-up, transmission surveillance of the immediate surroundings of leprosy individuals and in cases characterized with particularly pure nerve involvement which is difficult to diagnose or atypical lesions [71].

9.2.2. Hystopathology

The main pathologic feature is a granulomatous reaction. Epithelioid cells, macrophages, lymphocytes, plasmocytes and rarely neutrophil and mast cells are observed. Different granulomatous reactions occur according to the immune response of the host. While epithelial cells are mostly observed in TT and BT cases, foamy macrophages are observed mostly in LL and BL cases.

- *TL:* The reaction is mostly multifocal, periadnexal and perineural. Infiltrate is in dermis. The epidermis is usually atrophic. Giant langerhans cells are pathognomonic. Multinuclear giant cells can be seen while plasma cells are not expected to be observed. Perineurium is intact and is surrounded by lymphocytes. It can even infiltrate with granuloma structures. There is marked edema in the nerve tissue.
- **BT:** Findings are similar to those for TT. Epithelioid cells are less maturated, giant cells are undifferentiated and small. Epithelioid granulomas are less organized and tubercular structures are less prominent.
- **BB:** Epithelioid cells are immature. Organized epithelial granuloma structures are absent. Lymphocyte spread is diffuse and macrophages are quite over. Nerve tissue is not edematous. It has been infiltrated and partially destroyed by epithelial cells and lymphocytes.
- *BL:* Macrophage and lymphocyte predominant infiltration is present. Epithelioid cells are rare. Infiltration can be diffuse, nodular, perivascular and periadnexal. The epidermis and dermis are separated from each other by a narrow zone formed by the collagen. While macrophages contain more or less foamy cytoplasm, the formation of large vacuoles is not a feature of BL. The nerves have the onion skin perineurium.
- *LL:* The dermis is also characterized by diffuse macrophage invasion. There are no epithelioid cells. The epidermis is atrophic and has a very apparent grenz zone. Skin attachments are surrounded by macrophages and are atrophic. Macrophages contain gray cytoplasm with foamy changes. Large vacuolarizations can be seen. Perineural macrophage accumulation is present and perineum appears like onion skin. There is no sign of significant infiltration, and even the nerves can be quite normal. The nerves can be hyalinized or fibrotic [72].

9.2.3. Lepromin test

About 0.1 ml of lepromin antigen is administrated intradermally on to the forearm. The test is interpreted twice, first 24–48 hours and then 21 days. The first reaction is indicative of susceptibility, but may cross-react with other mycobacteria. The second reaction is resistance indicator to bacillus. Nodule >5 mm is considered positive. The most important point for the lepromin test is that it is not a diagnostic test, it should be used for classification and prognostic purposes.

9.3. Serology

M. leprae is stimulating cell-mediated abnormal response. Although the Ig that are formed are not protective, the importance of detection of the IgM formed towards PGL-1 (phenolic

glycolipid-1)-the only accessible test-is increasing day by day [67]. Search for effective diagnostic tests is accelerated by shifting the focus of the leprosy control strategy to early diagnostic and rapid treatment. Several studies have shown a correlation between serological titer and BI. The skin smear, the gold standard for classification, is thought to be a test that can be used as a support for clinical findings when histology is not possible [73, 74]. There was also a relationship between serology and reaction and relapse risk. Patients with a high PGL-1 Ig M level had a high risk of developing type 1 reactions [75]. In another study, post-treatment reactions were found to be more likely to develop in patients with positive serology after treatment [76]. In another important meta-analysis, seropositive healthy contacts were observed to develop three times more leprosy when compared to negatives [77]. In the light of these findings; additional studies are needed to determine serology, classification, early diagnosis, follow-up of disease, detection of individuals at risk, and determination of who should take prophylaxis among these individuals.

10. Management

10.1. Medical treatment

MDT is the key point of disease control. Dapsone, rifampicin and clofazimine are the first line drugs. Because of the increased drug resistance due to monotherapy and the ineffectiveness of each one on *M. leprae*, the use of multiple drugs was initiated in 1981 in line with WHO's recommendation. The use of dapsone, rifampin, and clofazimine (MB-MDT) is recommended for MB leprosy (BB, BL, LL), while dapsone and rifampin (PB-MDT) is recommended for TL, BT for 6 months since 1982. However, the duration of treatment for MB leprosy has changed over the years. The use of 12 months of MDT independent of smear is currently recommended, although formerly it was suggested that the treatment be continued until two consecutive negative skin smears are obtained [78, 79]. A single dose combination of rifampin 600 mg, ofloxacin 400 mg and minocycline 100 mg is recommended for patients with low baseline leprosy with a single lesion [80, 81]. Recommended doses are presented in **Table 1**.

Minocycline, clarithromycin and ofloxacin can be used as second-line drugs in MDT, where first-line drugs cannot be tolerated. Minocycline 100 mg/Daily can be used instead of dapsone and clofazimine, ofloxacin 400 mg/day instead of clofazimine, clarithromycin 500 mg/daily can be used where dapsone, clofazimine or rifampin cannot be tolerated [82].

WHO recommends that cases with a skin smear test +, or those without a definite diagnosis, are definitely treated with MB-MDT. Furthermore, attention should be paid to the fact that MB leprosy cases should not be treated with PB-MDT [81].

On the other hand, the National Hansen's Disease Programs (NHDP)—in the USA—involves different regimen. Treatment is recommended 12 months for PB leprosy and 24 months for MB leprosy. Furthermore, unlike the current regimen of WHO, rifampin is used daily rather than monthly [82]. Recommended doses are presented in **Table 1**.

	WHO recommended treatment regimens			NHDP recommended treatment regimens		
	Agent	**Dose**	**Duration**	**Agent**	**Dose**	**Duration**
	Tuberculoid (TT and BT)(paucibacillary)			*Tuberculoid (TT and BT) (paucibacillary)*		
Adult	Dapsone	100 mg/daily	6 months	Dapsone	100 mg/daily	12 months
	Rifampicin	600 mg/a month		Rifampicin	600 mg/daily	
Child[•]	Dapsone	50 mg /daily		Dapsone	1 mg/ kg/daily	
	Rifampicin	450 mg/a month		Rifampicin	10–20 mg/kg/daily (not >600)	
	Lepromatous (LL, BL, BB) (multibacillary)			*Lepromatous (LL, BL, BB) (multibacillary)*		
Adult	Dapsone	100 mg/daily	12 months	Dapsone	100 mg /daily	24 months
	Rifampicin	600 mg/a month		Rifampicin	600 mg/daily	
	Clofazimine	50 mg/daily and 300 mg/a month		Clofazimine	50 mg /daily	
Child[δ]	Dapsone	50 mg/ daily		Dapsone	1 mg/kg/daily	
	Rifampicin	450 mg/a month		Rifampicin	10–20 mg/kg/daily (not >600)	
	Clofazimine	50 mg/daily and 150 mg/a month		Clofazimine	1 mg/kg/daily	

[•]Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily and rifampicin 300 mg given once a month under supervision.

[δ]Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily, rifampicin 300 mg given once a month under supervision, clofazimine, 50 mg given twice a week, and clofazimine 100 mg given once a month under supervision.

Table 1. Recommended treatment doses of leprosy.

Moxifloxacin, pefloxacin, sparfloxacin, levofloxacin, and rifapentine that is a rifampin derivate are other agents with demonstrated efficacy [83, 84]. Clinical trials are needed in the long term.

Another treatment regimen studied is Uniform-MDT. It is the use for 6 months of dapsone, rifampin and clofazimine for patients with both PB and MB. However, the need for using additional clofazimine in PB patients and whether the treatment will be sufficient in MB patients are important questions present. This treatment is believed to set zero the risk of abduction of MB leprosy patients who received insufficient treatment by introducing a PB group [85]. In a study in which MB leprosy relapse was assessed in particular, relapse was found to be well below the targeted 5-year relapse rate of 5% [86]. Existing studies promises hope although further studies are needed [87, 88].

10.2. Treatment of immunological reactions

10.2.1. Type 1 reaction

Supportive therapies such as parol, non-steroidal anti-inflammatory drugs (NSAID), can be administered if there are no neuritis findings such as pain, function, or sensory loss. If nerve involvement is present, prednol 0.5–1 mg/kg/day peros is the first choice treatment. When the reaction is relieved, the dose is slowly reduced so that it remains above the dose of 0.25 mg/kg/day for at least 3–6 months. In ongoing process, dose reduction is continued with careful follow-up of nerve functions [89]. Cyclosporin is another option when steroids are not usable [90, 91]. In a study in which azothioprine was assessed, efficacy in type 1 reaction was not demonstrated [92].

10.2.2. Type 2 reaction

The incidence of type 2 reaction has decreased after addition of clofazimine to MDT with anti-inflammatory effect [93]. If there is no findings of neuritis, supportive treatment care such as NSAID (aspirin, indomethacin) and paracetamol may be administered. Prednol (0.5–1 mg/kg/day) is the first choice if neuritis is present. Once the reaction is decreased, the dose should discontinued by reducing the dose in time. However, frequently the reaction relapse during dose reduction. In this case, thalidomide, clofazimine and pentoxifylline can be used as adjuvants. WHO recommends to start by using clofazimine 3 * 100 mg (300 mg/day) and then reduces to 100 mg/day. It should not be used for type 2 reaction as a single agent and for more than 12 months. Reaction can be rapidly controlled by using thalidomide 300–400 mg/day. Dosage may be reduced to 100 mg/day for extended periods of usage. Since it is teratogenic, attention must be paid to the use in women who has childbearing potential [81]. Pentoxifylline is used as 3 * 400 mg. In a study that compares the efficacy of clofazimine and pentoxifylline, pentoxifylline effectively reduced the initial severity, while clofazimine showed a slow but sustained effect [94]. Resistant erythema nodosum leprosum cases that treated successfully with methotrexate, infliximab and etanercept have been reported [95–97].

11. Follow-up

WHO aims to follow the patients up monthly by 28-day drug supply. In regions where monthly follow-up is difficult, it is recommended that more than a monthly dose be given and

train family members or nearby people for observation purposes [81]. On the other hand, the NHDP recommends first follow-up on 1st month and then with 3 months periods. Reaction therapy should be followed up closely. Disease progression is largely due to incompatibility to treatment. Complete information about possible reactions, complications, drug side effects should be provided and the patient and his/her relatives compliance to treatment should be ensured. At each follow-up, laboratory tests for drug toxicity are recommended with full clinical evaluation including nerve examination. While complete blood, urea, creatinine, AST, ALT follow up is adequate, it is advisable to check glucose 6 phosphate dehydrogenase level for once for dapsone usage before treatment, if possible. A yearly skin smear or biopsy is recommended to follow the bacteria burden. After treatment, it is advisable to follow up at least 5 years of PB cases and 10 years of MB cases [82, 98].

Existence of persister strain, insufficient/inappropriate treatment, monotherapy, drug resistance, high BI at diagnosis, number of lesions and lepromin negativity are factors that increase relapse risk. The risk of relapse after MDT has decreased considerably. In a study of 3248 patients followed for 16 years, cumulative relapse rates after MDT were 1.78% [99]. The relapse rate was 6.1/1000 person years in one of the last current studies in which 2177 patients are followed up [100]. To reduce the risk of relapse, individualization of treatment duration is recommended in individuals predicted to be at high risk for relapse [101].

11.1. Drug resistance

Drug resistance is the result of leprosy-resistant transmission (primary resistance) or mutation-induced secondary resistance which develops under treatment [102]. *FolP1, rpoB, and* gyrA gene mutations are associated with dapsone, rifampicin and ofloxacin resistance. Gene sequencing by PCR is a rapid and sensitive method to demonstrate drug resistance [103]. Due to the lack of effective second-line drugs; resistance to first-line drugs is a matter of concern to the WHO Global Leprosy Program. In 2008, drug resistance global surveillance was initiated to assess the efficacy and drug resistance level of the current leprosy control strategy. Eighteen reference centers have been established in 18 pilot countries and mutation detection by PCR has begun. Obtained data suggest that resistant *M. leprae* does not pose a risk for current disease management [104, 105].

12. Elimination/prevention

With MDT, in 1985, with 5.1 million leprosy cases falling to 3.1 million in 1991, WHO aimed to eliminate leprosy worldwide in 2000. Elimination target was 1/10,000. Countries like India and Brazil have been under the target even though the target has been reached substantially around the world. Although Brazil is one of the last countries to reach the goal today, endemic areas like Chhattisgarh, Pará and Madura are still far behind the target. On the other hand, in spite of successful elimination program, WHO declared in 2013 that leprosy control is faltered due to the plateau of the incidence of leprosy until 2005, the new diagnosis of leprosy cases with G2D remain constant between 2010 and 2013, and the number of new cases in children is not decreasing. In addition, late-diagnosis-related disability-ending stigmatization of leprosy patients continued. Epidemiological data showed that the

prevalence-based elimination program could not stopped the spreading. The meeting was held in Brazil in 2015 and the strategy was changed. A strategy based on incidence instead of prevalence was identified. Early diagnosis and prompt inclusion of all patients to treatment were aimed [30, 106, 107].

Living in the same house with a leprosy person increases the risk of spreading by 2–10 fold. Most of the new cases constitute subclinical infection cases in contact and no diagnosed cases. For this reason, for eliminating leprosy, it is very important to detect new cases with effective contact monitoring. The development of diagnostic tests that can detect subclinical infection and separate exposure to and infection with *M. leprae* is very important [101, 108].

12.1. Immunoprophylaxis/chemoprophylaxis

In fact, BCG, which is tuberculosis specific, is the only vaccine used for leprosy protection. The level of protection, as well as the protection against leprosy is evidenced, varies between 20% and 90% in the literature. Protection level of the vaccine, when vaccinated in first decade, was higher in women and lower socioeconomic individuals [109]. With age, the level of protection decreases [110]. Although it has been shown that revaccination of leprosy patients and contacts with them have been shown to reinforce the protection, this approach is still not common and there is a need for studies evaluating efficacy [39, 111].

Protection of post-contact chemoprophylaxis (PEP) has been shown in clinical trials in a range of 35–57% in patients with asymptomatic contact. Although it is not included in WHO's official recommendations, PEP evaluations rapidly continue with a single dose of rifampin (SDR). One study has shown that the protection of PEP with BCG combination is better in distant-contact individuals [112]. With the cooperation of Novartis agency and Netherlands Leprosy Relief (NLR), Leprosy Post-Exposure Prophylaxis (LPEP) program has been established. A large-scale study was started to investigate the applicability of the use of SDR as a PEP by the program and the impact on the number of new diagnosed cases. It is expected that the first data will be obtained in 2019 [113].

12.2. Prevention of disability

Permanent nerve damage is a part of the natural process of the disease, and the risk is also quite increased with leprosy reactions. Reducing the stigmatization of leprosy patients and providing mental well-being is possible by preventing nerve damage. Delay in recognition of leprosy and leprosy reactions, and therefore of delay in treatment is the most important factor on permanent nerve damage. Follow-ups should be done in leprosy centers whenever possible. It is important to ensure compliance with treatment and follow-up. Patients should be educated on issues such as care of existing wounds, proper shoe selection, self-examination of hands and feet. Another important point is that the leprosy does not come to mind because of the rare occurrence in some areas and the patients are followed up with false diagnoses. The implementation of information programs for healthcare professionals is also important in this context [114–116].

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