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A Review: Leprosy, Hansen's Disease

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ABSTRACT

Leprosy, a chronic, infectious disease caused by *Mycobacterium leprae* (*M.leprae*), commonly known as Hansen's disease, and has been known since biblical times. It is still endemic in many regions of the world. Global incidence remains high and patients often have long-term complications associated with the disease. The mechanism of transmission of leprosy consists of prolonged close contact between susceptible and genetically predisposed individuals and untreated patients. Transmission occurs through inhalation of bacilli present in upper airway secretion. The nasal mucosa is the main entry or exit of *M.leprae* Bacilli multiplies very slowly and an average incubation period of about 5 years. Symptoms can last up to 20 years. Based on body index leprosy can be classified as paucibacillary (PB) and multibacillary (MB). The Indian classification includes mainly 4 groups of classification namely, indeterminate, tuberculoid, lepromatous, and borderline leprosy. *M.leprae* preferentially attacks Schwann cells. Disease and development depend on many factors, including immune function and genetic predisposition. T-lymphocytes have a key role in the pathogenesis of leprosy. Leprosy is curable and prevented if treated earlier. Multidrug therapy (MDT) has been made available by WHO free of cost to all patients worldwide since 1995, a highly effective cure for all types of leprosy.

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INTRODUCTION:

The term Leprosy is a salute to the Norwegian physician Gerhard Armauer Hansen, who identified the bacillus Mycobacterium leprae (M.leprae) as the origin of the disease in 1873. [1, 2, 3, 4, 5, 6]Leprosy is a chronic infectious disease caused by Mycobacterium leprae. [4, 6, 7, 8]M.leprae, an acid-fast bacillus is a major human pathogen.[4, 6]It is extremely contagious, but its morbidity is less since a large extent of the population is generally resistant to this disease. Leprosy affects most of the skin and peripheral nerves. [1, 2, 5, 7, 8, 9]The disease ranges from a singular patch or single nerve thickening to the diffuse involvement of the skin, multiple nerves, and even the internal organs. [2]The neurological involvement in leprosy results in sensory-motor deficits leading to deformities and disability. [2, 5, 6]Early diagnosis is very important. [1]A lack of awareness about the signs and symptoms of the disease makes the diagnosis of leprosy very challenging. [2] Upper airways are the main entry door for the bacillus and the route for bacillary elimination. [9] M. leprae multiples very slowly and the average incubation period of the disease is about 5 years. [4,7] M. leprae infected individuals that present clinical symptoms remain at risk of developing nerve damage. [5]The mechanism of transmission of M. leprae is not known. [10]The introduction of dapsone therapy in the late 1940s was the first effective treatment for leprosy, and this was followed by the move to short-course multidrug therapy (MDT) in 1981. [7]The introduction of multiple drug therapy (MDT) in 1982 has caused a decrease in the prevalence of leprosy worldwide. [5, 6, 7, 8, 10]

Epidemiology

Leprosy, from an epidemiological point of view, is a disease with various interesting features. Among these, one should mention its high infectivity and low pathogenicity, its prolonged incubation period, and its high tendency for spontaneous healing, in addition to its extensive range of manifestations. [11]

Geographic distributions: The estimated total number of leprosy patients in the world, made by WHO in 1975, varies from 10-12 million. [11, 12]

Of the estimated cases, Asia contributes to the largest share with about 62%, followed by Africa with about 34%, South America with about 3%, and the rest of the world with about 1%. However, in terms of prevalence by continent, the problem is about 3 times as intense in

Africa as it is in Asia. Almost 1 billion people in the world live in high endemic areas where the prevalence of leprosy is at least 1 per 1000. [12]

The new case detection rate for leprosy remains high, with about 250 000 new cases being registered annually. Around 15 million people have been treated with multidrug therapy, and an estimated 2 million people have been prevented from developing disabilities. [13, 14, 15]

The WHO publishes an annual report on the worldwide incidence of leprosy, including the number of new cases, prevalence, and disabilities. The detection of new cases by the WHO has declined from 514 718 (2003) to 244 796 (2009), but the rate of decrease is getting smaller each year. Among 244 796 new cases in 2009, 16 countries that reported 1000 or more new cases accounted for 93% of the total. [13, 14, 15]

Very few new leprosy patients are registered in developed countries. When leprosy is detected, it is primarily found among immigrants from countries where the disease is still endemic. [13, 15]

Age Distribution: The generally described age pattern of leprosy incidence rates: a peek at ages 10–14 years followed by a depression which in turn is followed by a rise and a plateau covering ages 30–60. [12, 15, 16]

Sex Distribution: Males are affected more frequently than females, often in the ratio of 2:1. This reported male excess could be the result of a difference in examining males and females or to unequal availability of health services for men and women. The male preponderance is much more pronounced in lepromatous leprosy than in tuberculoid leprosy. [12, 16, 17]

Society distribution: Expatriate races show forms of leprosy more similar to those prevailing in their native lands than those amongst the natives of the land in which they live. Different groups in multiracial societies vary in the ratios of the different forms of leprosy and their detailed manifestation. [12, 18, 20]

Genetic distribution: Quantitative comparisons between populations of the frequency of different forms of leprosy varies according to the methods of classification used. Populations are polymorphic concerning their reactions to the lepromin test; this may indicate genetic variation. Affected individuals within families tend to suffer from similar forms of leprosy. The evidence suggests that there is a genetic system in man which affects the form that leprosy might take. There is a possibility that genetic variability in the M. leprae influences

the manifestation of leprosy. Neuritic leprosy accounted for 1 0·7% of all paucibacillary cases in the present series. [12, 15, 18, 19, 20, 21, 22]

Etiology

Leprosy is a chronic infectious disease that is endemic in tropical and subtropical regions, where it afflicts 10 to 15 million persons. [23]

• **Causative agent**: Leprosy is caused by the obligate intracellular parasite Mycobacterium leprae. [1, 23, 24, 25, 26] It is also called Hansen's bacillus. [1] . It is not very infectious (difficult to transmit) and has a long incubation period (time before symptoms appear), which makes it difficult to determine where or when the disease was contracted. Children are more susceptible than adults to contracting the disease. [26] M. leprae's taxonomy is as follows: class Schizomycetes, order Actinomycetales, family Mycobacteriaceae, and genus Mycobacterium. M. leprae is a straight or moderately curved rod, with rounded ends, measuring 1.5-8 microns in length by 0.2-0.5 micron in diameter. [1] M. leprae is an acid-fast bacteria, M. leprae look red when a Ziehl-Neelsen stain is used. [1, 26] In 2008, a new etiologic agent namely, Mycobacterium lepromatosis was recognized in two patients of Mexican origin who died of diffuse lepromatous leprosy (DLL). [24, 26]

• Leprosy is caused/contracted by the following:

1. Person to person-leprosy spread from person to person through infected respiratory droplets;

2. Parents of someone with leprosy;

3. Children of someone with leprosy;

4. Brothers or sisters of someone with leprosy;

5. The extent of exposure;

6. Genetics;

7. Environmental conditions. [26]

Risk Factors of Leprosy

Leprosy is a communicable disease that can lead to physical disabilities, social stigma, and great hardship. Effective treatment has been available since 1960, but early diagnosis of the disease remains the foremost effective way to stop the transmission chain and avoid late diagnoses and subsequent disabilities. Knowledge of the risk factors for leprosy can facilitate early detection. [27]

1. Contact with the infected:

Contacts of patients with leprosy have an increased risk of contracting leprosy than does the general population. The most important known determinant for contracting leprosy is being a household contact of a leprosy patient, which carries a 5 to 8 times higher risk of contracting leprosy.

This higher risk is a consequence of the high bacillary load pressure of the LL index case on their contacts and possible familial genetic factors. [36, 27, 28, 29, 30, 31, 32]

2. Living in endemic areas:

Leprosy is still endemic in developing countries, like Brazil, India. 85% of the world's patients live in six countries (India, Brazil, Nepal, Myanmar, Mozambique, and Madagascar. However, in endemic regions, the majority of new leprosy patients are not close contacts of a known leprosy case. Prolonged contact with immigrant individuals or with non-immigrant individuals that frequently travel to endemic regions poses as a risk factor. [27, 28, 32, 33, 34]

3. Exposure to armadillos:

Multiple autochthonous cases of leprosy have been reported in the USA and several of them have been attributed to zoonotic transmission from armadillos. Patients are found to have M. leprae strain 3I-2-v1, which may exist in most infected armadillos. [30, 33]

4. Poverty and Related Factors:

Poverty has been considered as a risk factor for leprosy and is related to nutritional deficiencies. Inadequate intake of nutrients due to food shortage may affect the immune system and influence the progression of infection to clinical leprosy.

Low education level, food shortage, water shortage, bathing weekly in open water bodies (creek, river, and/ or lake) 10 years previously, and a low frequency of changing bed linen or hammock currently were all significantly associated with leprosy. [27, 28, 30, 32, 35]

5. Age and sex of contact:

There is an increased risk from age 5 to 15 years that peaks between age 15 and 20 years, followed by a decreased risk from age 20 to 29 years. After age 30 years, the risk again increases gradually. Men have a two times higher risk of contracting leprosy than women although both sexes are equally susceptible. [27, 31, 34, 36, 37, 38]

6. Type of leprosy of the patient:

Patients with MB leprosy have 5-8 times higher risk than contacts of patients with PB leprosy. Patients with PCR positive nasal swabs are probably patients with the highest transmission potential. Seropositive persons have 3-8 times higher risk than seronegative persons. [27, 29, 31, 34, 37]

7. Genetic polymorphisms of the IL6 and NOD2 genes are risk factors for inflammatory reactions in leprosy. [38]

Classification

Several classifications are intended for leprosy over the years. The Madrid classification, established within the International Leprosy Congress, was held in Madrid in 1953. [1, 39, 40, 41]This system is predicated on the clinical characteristics and therefore the result of skin smears.[1] The arrangement of Ridley & Jopling(1962,1966)uses the concept of spectral leprosy supported clinical, immunological, and histopathological criteria.[49]The Ridley Jopling system classifies leprosy as an immune-mediated spectral disease with tuberculoid leprosy(TT)at one end of the spectrum and lepromatous leprosy(LL)at the opposite end. These two ends of the stretch are considered to be clinically firm. [1, 2]In 1982, the WHO, with operational and therapeutic purposes, established a simplified classification supported the bacterial index (BI). According to this classification, leprosy was divided into paucibacillary(PB)and multibacillary (MB), and PB patients are those that have a BI lower than 2+, and MB patients are those showing a BI above or adequate to 2+. [1,2]. The Indian classification includes 4 groups: (a)tuberculoid, (b)borderline, (c)lepromatous, (d)indeterminate.[51]

a) Indeterminate Leprosy: Indeterminate leprosy presents as single, slightly hypopigmented, or faintly erythematous and typically hazy macules on the skin. A sensation in the affected area is slightly damaged while sweating and hair growth are usually unaltered. The peripheral nerves are normal. Slit skin smears are mostly negative. Indeterminate leprosy is typically self-limiting, self-curing. [1, 2, 3, 39, 41]

b) Tuberculoid Leprosy: Tuberculoid lesions could also be reddish or brownish or hypopigmented. Well defined edges and sensory loss, i.e.loss of feeling for pain and/or touch and temperature, are characteristic features of tuberculoid leprosy. The affected area is symptomless(e.g.no itching), rough and either hairless or with sparse hairs and should show central healing, tuberculoid leprosy is usually stable. [1, 2, 3, 39, 40]

c) Lepromatous Leprosy: during this form, M.leprae multiplies and spreads through the blood due to the absence of cellular immune reaction to the bacillus. Skin lesions tend to be multiple and symmetrical, preferably located within the colder areas of the body, characterized by hypochromic, erythematous, or bright brownish spots with indefinite borders. These spots might not have a loss of sensation. [1, 2, 3, 39, 40]

d) Borderline leprosy: Globally, the borderline form contributes to the bulk of the disease burden thanks to leprosy. Nearly always hypopigmented, lesions are strictly macular. Immunologically, the disease is unstable. [2, 3, 39, 40]

Pathophysiology

Leprosy transmission is not completely understood, but it is believed to spread through respiratory means. Untreated individuals with lepromatous infections usually contain many bacilli. The general model of dissemination, once within the body, starts at the upper respiratory tract. Reports indicate that host infection can potentially occur through broken skin as well. [42] M. Leprae has a predilection to Schwann cells and skin macrophages and host response is important in determining the outcome of infection. [4, 5] There are three important aspects of leprosy pathogenesis: The spectrum of the immune response, nerve damage, and immune-mediated reactions. [4] Several pathogenic mechanisms may be responsible for nerve damage in leprosy, including biochemical interference of M. leprae with host cell metabolism, mechanical damage due to the large influx of cells and fluid, or immunological damage. Unfortunately, however, when infected Schwann cells are killed as well, this may lead to nerve damage, which may progress to irreversible loss of peripheral

nerve tissue. [5] M. leprae's affinity for peripheral nerve cells, preferentially attacking Schwann cells (SCs), causes nerve demyelination and loss of axonal conductance, which presents clinically as numbness. [6, 42] Among bacterial pathogens, infection of peripheral nerves is a unique property of M. leprae. Infection of peripheral nerves is the sine qua non of leprosy, but many clinical details regarding the frequency and extent of nerve injury have only recently been described, and the mechanism(s) underlying nerve injury in leprosy is very poorly understood. [10] The disease's growth and development depend on many factors, including immune function and genetic predisposition. [42] Immune-mediated responses are responsible for leprosy reactions. [4] T lymphocytes have a key role in the pathogenesis of leprosy. [43] Th1 immune response is strong and is associated with lower bacterial counts and limited disease, whereas Th2 response is weak and results in higher bacterial counts and more severe disease. [42] Lepromatous patients have a specific cell-mediated T-cell and macrophage energy to M. Leprae antigens in-vitro. They are negative on lepromin skin testing. Tuberculoid patients possess Th-1 type response to M. Leprae producing interleukin-2 and interferon-γ (INF-γ) and positive lepromin (a soluble Leprosy bacillus antigen) skin tests. [4] Tuberculoid leprosy is a mild form of the disease and is limited to a few hyperesthetic and hairless skin plaques. It is characterized by cell-mediated immunity with mainly type 1 helper T cell (Th1) immune response and CD4+ T cells. Lepromatous Leprosy is characterized by cell-mediated immunity with mainly type 2 helper T cell (Th2) response and CD8+ T cells. [43]

Diagnosis

Leprosy is characterized by a long and variable incubation period and a chronic clinical course. [44] The diagnosis of leprosy is essentially based on clinical features of skin lesions, nerve involvement, and BI (bacterial index by acid-fast staining), and histopathological methods. [44, 45, 46] PB patients have one or a few skin lesions and a low or absent BI and demonstrate specific cell-mediated immunity against M. leprae, but they have low or absent titers of M. leprae-specific antibodies and granulomatous dermatopathology. In marked contrast, MB patients have multiple symmetric skin lesions and a high BI and demonstrate high titers of anti-M. leprae antibodies but an absence of specific cell-mediated immunity and dermatopathology largely devoid of functional lymphocytes. [45, 47, 48, 49] The presence of serum immunoglobulin M (IgM) antibody to phenolic glycolipid I (PGL-I) correlates with BI in leprosy patients and has been used to support disease symptoms as a means to categorize leprosy patients. [46, 47]

METHODS

1. ELISA test

Enzyme-linked immunosorbent assay (ELISA) and rapid lateral flow test formats have been developed for the detection of anti-PGL-I antibody. [46, 47, 48, 50, 51]

2. Differential diagnosis

The differential diagnosis of leprosy has been performed based on clinical criteria and the presence of acid-fast bacilli (AFB) from tissue smears or tissue sections stained by Ziehl–Neelsen or Fite–Faraco methods. [45] Slit-skin smears can also be taken from both ear lobes. All smears should be prepared on microscopic slides, stain by the classic Ziehl– Neelsen method, and observe by well-trained technicians to identify AFB. By this method, BI and morphological index (MI) can be evaluated according to Ridley's logarithmic scale. MI is the percentage of solid bacilli in the samples. [44, 45]

3. Polymerase chain reaction (PCR) technique

PCR is a sensitive and specific method that provides a promising approach for early diagnosis and treatment, leading to the possible reduction of permanent deformities and disabilities and a reduced socioeconomic burden due to leprosy in endemic countries. [45] PCR for M. leprae DNA may be a very early detection test for leprosy. [52] The use of PCR is to detect several regions of Mycobacterium leprae DNA in skin smears and skin and nerve biopsies may be used to provide an accurate diagnosis, which is fundamental for leprosy management, prevention of disability, and epidemiological statistics. The greatest advantage of PCR is its high sensitivity and specificity, with no need for bacterial culture. [51]

4. PCR amplification

New molecular biology methods, PCR amplification, have been developed as reliable and sensitive diagnostic tools for the detection of pathogens in leprosy. Several investigators have used PCR to amplify various genomic sequences of M. leprae to improve the detection of low numbers of bacteria. [45, 46]

5. Histopathological examination (Skin biopsy)

Histopathological detection of M. leprae usually provides superior sensitivity over slit-skin smear detection of M. leprae. [44, 45] An improvement of the M. leprae DNA detection in

skin biopsy is by using a set of primers that amplify a 130-bp amplicon with high sensitivity and specificity. [51]

Treatment

Over the centuries leprosy has remained a feared disease with severe social repercussions for the sufferers. Until the Second World War, no effective treatment was available; health authorities had to resort to segregation to prevent the spread of the disease. This may have had some effect on leprosy endemic, but in general, it only increased suffering and stigmatization. [53] Some of the drugs which are used in treating Leprosy are:

- Dapsone- is consistent with a more rapid killing action by rifampicin. [54] Dapsone is well-tolerated by mouth administration. [55, 56] Improvement under dapsone treatment are cutaneous ulcers heal, nose becomes clear, febrile reaction and the appearance of transient nodules gradually gets less and disappears. [56]

- Promin- The sodium salt of p. p. diamino-diphenyl sulfone and dextrose sulfonate, used in the treatment of leprosy. [57] Promin can be given orally or intravenously. By oral administration, it is more toxic, and much larger doses are tolerated by the intravenous route. [57, 55, 56]

- Diamino-Diphenyl sulphone (D.A.D.P.S)- was the first sulphone synthesized (Fromm and Wittmann 1908), but its pharmacology and therapeutic effects were not studied until 1937. D.A.D.P.S. mainly occur-in the gut before absorption, when the drug is given by the mouth; or in the body fluids or cells after absorption from the gut or, in the case of injection, from the tissues. [55]

- "B 663" (clofazimine)- is a Rimino-compound which has very high anti-tuberculosis activity in vitro, and some anti-tuberculosis and anti-leprosy activity in vivo. It has a definite effect on lepromatous leprosy, causing an improvement in the clinical state, a concurrent fall in the Bacterial Index, and this effect is enhanced by the addition of standard doses of dapsone. [58]

MULTI DRUG THERAPY- The WHO study group recommended MDT in 1982 because of increasing resistance to dapsone. MDT consists of three drugs: dapsone, rifampin, and clofazimine. [53, 59, 60]

Rifampicin proved to be extremely effective and showed high activity against experimental leprosy, inhibiting the multiplication of dapsone-sensitive and dapsone-resistant strains of M. leprae. [53, 54, 60]

Clofazimine is weakly bactericidal and has some anti-inflammatory action. In combination, dapsone and clofazimine potentiate each other and the use of triple combination therapy hinders the possible development of rifampin drug resistance. [60]

Table 1:Drugs used in the treatment of Multibacillary and paucibacillary Leprosy.

Sl no	Classification	Medication	Duration (6months)	Quantity Per Day	Adult doses[50-70Kg]	Child doses[10-14 yrs]
01	Paucibacillary	Rifampicin Dapsone	Once in a month	2 capsules 1 tablet	300mg*2 100mg	300mg+150mg 50mg
		Dapsone	Once a day	1 tablet	100mg	50mg
02	Multibacillary	Rifampicin Clofazimine Dapsone	Once a month	2 capsules 3 capsules 1 tablet	300mg*2 100mg*3 100mg	300mg+150mg 50mg*3 50mg
		Clofazimine Dapsone	Once a day	1 capsule 1 tablet	50mg 100mg	50mg 50mg

*For children younger than 10, the dose must be adjusted according to body weight

WHO worked in shortening the treatment duration of MDT for MB patients from 24 to 12months, thus improving the statistics, especially in countries with a high percentage of MB patients. [53]

Several reactional states can occur as a result of altered immune responsiveness. At least 50% and possibly a much higher percentage of HD patients will experience reactional states after initiating therapy. Nerve damaging reactions are the cell-mediated Type I leprosy reaction (RR) and the Type II leprosy reaction (ENL), which seems to be immune-complex driven. [53, 59, 60]

CONCLUSION:

Leprosy is a complex infectious granulomatous disease that causes peripheral nerve injuries by modulating the host immune response. The pathogenesis of leprosy is complex and multifactorial, including genetic susceptibility to the infectious microorganisms M. leprae, molecular mimicry of Mycobacterium leprae proteins to host proteins and host adaptive and cell-mediated immunity. The early diagnostic is critical for the prevention of deformities and disabilities and also very important for a better quality of life for patients with leprosy. Educating the people regarding this disease and its symptoms and complications can lower the risk of this disease to spread in the future; by taking preventive measures educating the people regarding symptoms and treatment of leprosy. Hopefully, the tremendous progress seen in the past decades in controlling this disease and defining the causative organisms will lead to further advances and prevention of infection.

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