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A General Overview of Leprosy

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ABSTRACT
Leprosy is clinically characterized by one or more of the three cardinal signs: hypopigmented or erythematous skin patches with definite loss of sensation, thickened peripheral nerves, and acid-fast bacilli detected on skin smears or biopsy material.Mycobacterium leprae is one of the last bacterial species of medical interest that cannot be cultured in vitro (mainly because of its reductive genome evolution), and transmission and pathophysiological data is still limited.The susceptibility to the mycobacteria and the clinical course of the disease are attributed to the host immune response, which heralds the review of immunopathology of this complex disease.

Keywords: Leprosy,Mycobacterium Leprae, Microorganism, Pathogenisis, Cases, Incubation Period, Epidomology, Pathophysiology, Complications, Treatment, Diseases,World Health organisation (WHO).

INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by Mycobacterium leprae, a microorganism that has a predilection for the skin and nerves.Though nonfatal, leprosy is one of the most common causes of nontraumatic peripheral neuropathy worldwide. The disease has been known to man since time immemorial.In 2005, the World Health Organization (WHO) reported that leprosy was eliminated as a world public health problem. However, new cases are still seen to this day.

Globally, to date, an average of 250 000 new patients are reported annually. Incidence and prevalence of this condition differs considerably per country, noting that developing countries bear the biggest brunt of both new cases and that of patient on treatment.

Leprosy is a very old disease, which spreads through the centuries via the various populations of the world. The first 3 large clusters of leprosy were found in India, China, and Egypt.The first biological evidence of leprosy found in humans was identified thanks to paleontology and its use of molecular biology. The DNA of M. leprae was isolated from the bones of a man skeleton dating from the 1st century BC and found in a grave near Jerusalem.

The first medical description of leprosy was found in an Indian treaty, known as the Sushruta Samhita, dating from 600 BC. In China, the first clinical description consistent with leprosy dates from the 3rd century BC. In India, 4 skulls with leprosy-specific lesions were found and dated to be from the 2nd century BC[1].

Classification of leprosy

Tuberculoid leprosy

Tuberculoid leprosy is defined by skin lesions and nerve damage. Skin manifestations either include large hypochromic macules with well-defined edges that can sometimes be infiltrated, or large thickened and infiltrated plaques. Tuberculoid leprosy presents with very few lesions (hyposensitivity or anesthetic lesions). Nerve damage is usually observed around skin lesions and is associated with sensory and/or motor impairment when the hands and feet are affected[2].

Lepromatous leprosy

The initial skin lesions are small-sized hypochromic macules with indistinct edges. If left untreated, they form copper colored papules or nodules known as leproma. Lepromatous leprosy patients present with a high number of bilateral and symmetrical leproma (20 to 100) that can develop everywhere on the skin but most frequently on the face, earlobes, fingers, and toes. Those lesions are not anesthetic. Peripheral nerve damage is often bilateral, diffuse, and symmetrical. It is associated, to various extents, with peripheral nerve hypertrophy, sensory and/or motor impairment.

Borderline leprosy

Borderline leprosy is defined by various clinical signs and corresponds to a transition status. Its classification depends on the number of clinical

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signs consistent with tuberculoid or lepromatous lesions. The borderline tuberculoid (BT) presentation of leprosy is defined by the presence of several large asymmetrical and hypoesthetic lesions with peripheral macules or infiltration of the skin. Smaller lesions can usually be observed near the larger ones. The borderline–borderline (BB) presentation is defined by the presence of several nonanesthetic annular lesions with indistinct edges. The borderline lepromatous (BL) presentation is defined by the presence of more than 10 bilateral and non-anesthetic lepromas and annular lesions[2].

Epidemiology

The number of leprosy case patients detected every year between 2000 and 2006 significantly decreased from 719,219 case patients in 2000 to 265,661 in 2006. The decrease was mainly due to the lower number of leprosy case patients identified in the regions of the world that are still reporting the highest number of case patients.Unfortunately, this decrease in annual case patients started to drastically slow down in 2006: 265,661 case patients were reported in 2006 and 215,656 in 2013.The proportion of women among newly detected leprosy case patients in countries reporting more than 100 new case patients per year was lower than that of men, ranging from 0.5% (Pakistan) to 56.4%.

The latest available data suggests that the overall prevalence of leprosy case patients in countries that are still reporting case patients is 0.32 per 10,000 population.. Over the past 20 years, the WHO implementation of MDT has rendered leprosy a less prevalent infection in 90% of its endemic countries with less than one case per 10,000 population. Though, it continues to be a public health problem in countries like Brazil, Congo, Madagascar, Mozambique, Nepal, and Tanzania[3].

Pathogenis

Pathogenesis of type II reaction is thought to be related to the deposition of immune complexes. Increased levels of TNF-α, IL-1β, IFN-γ, and other cytokines in type II reactions are observed. In addition, C-reactive protein, amyloid A protein, and α-1 antitrypsin have also been reported to be elevated in ENL patients' sera. A massive infiltrate of polymorphonuclear cells (PMN) in the lesions is only observed during ENL and some patients present with high numbers of neutrophils in the blood as well. Neutrophils may contribute to the bulk of TNF production that is associated with tissue damage in leprosy.

More recently, microarray analysis demonstrated that the mechanism of neutrophil recruitment in ENL involves the enhanced expression of E-selectin and IL-1β, likely leading to neutrophil adhesion to endothelial cells; again, an effect of thalidomide on PMN function was observed since this drug inhibited the neutrophil recruitment pathway.

Altogether, the data highlight some of the possible mechanisms for thalidomide's efficacy in treating type II reaction. TNF-α may augment the immune response towards the elimination of the pathogen and/or mediate the pathologic manifestations of the disease. TNF-α can be induced following stimulation of cells with total, or components of M. leprae, namely, lipoarabinomannan (the mycobacteria "lipopolysaccharide-" like component) a potent TNF inducer.

In addition, mycolyl-arabinogalactan-peptidoglycan complex of Mycobacterium species, the protein-peptidoglycan complex, and muramyl dipeptide all elicit significant TNF-α release.

M. leprae is an acid-fast, gram-positive obligate intracellular bacillus that shows tropism for cells of the reticuloendothelial system and peripheral nervous system (notably Schwann cells).Organisms may be acquired by the susceptible host usually through respiratory system or by way of skin to skin contact (between exudates of a leprosy patient's skin lesions and the abraded skin of another individual).

It has low pathogenecity, only a small proportion of infected people develop signs of the disease with incubation period varying from 6 months to 40 years or longer.After entering the body, bacilli migrate towards the neural tissue and enter the Schwann cells.Toll-like receptors (TLRs) also play important role in the pathogenesis of leprosy.TLRs, such as TLR-1 and TLR-2, are found on the surface of Schwann cells, especially inpatients with tuberculoid leprosy[4].

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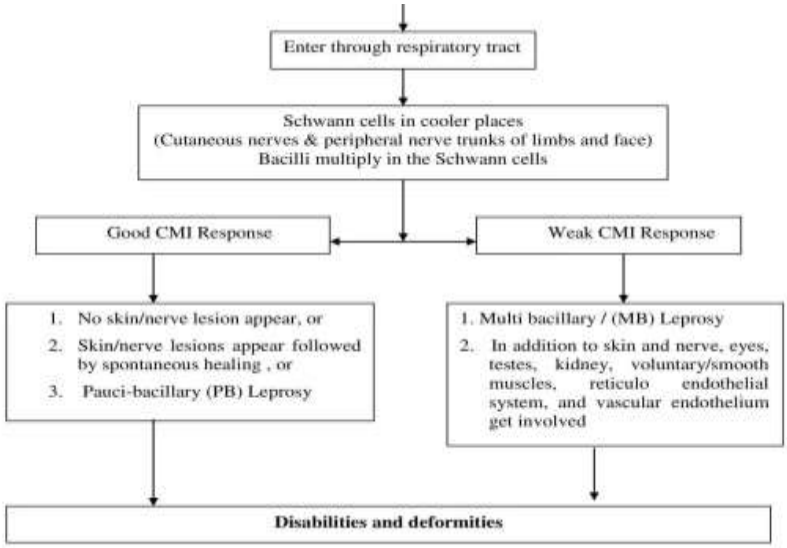

Figure 1: Pathogenesis of Mycobacterium leprae

Pathophysiology

Leprosy is probably transmitted through nasal or sputum excretions. The results of experimental studies conducted on mice pointed out to the respiratory tract as a potential portal of entry for bacilli instead of the digestive tract or the skin.

Studying the incubation period of leprosy is not easy because of (i) the insidious nature of the disease, especially in the early phase, (ii) its slow evolution, and (iii) the absence of sensitive and specific diagnostic tests for the sub-clinical phase of the infection. Various incubation periods have been reported: very short ones in young children (3 and 6 months old) [, or very long ones (up to 30 years) . The short incubation period was observed in 2 leprosy patients with a bacilli count respectively performed 4 months and 15 days before the first signs of lepromatous skin lesions . The longer incubation periods were observed in American war veterans who used to be stationed in endemic countries for short periods of time. These incubation periods ranged from 2.9 to 5.3 years for patients presenting with tuberculoid leprosy and from 9.3 to 11.6 years for patients presenting with lepromatous leprosy[5].

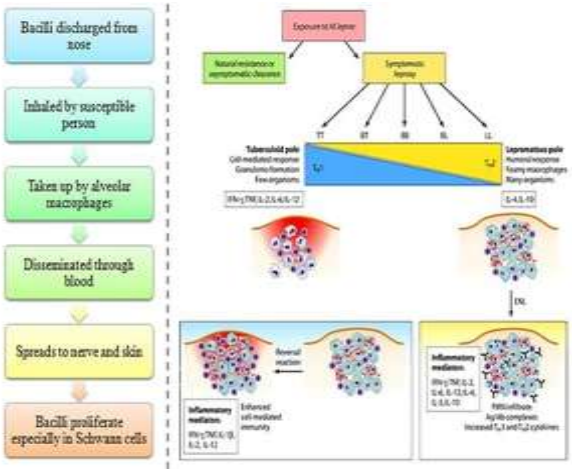

Figure 2: Pathophysiology of Mycobacterium leprae

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Histopathological Reactions

Histopathologically, skin lesions from tuberculoid patients are characterized by inflammatory infiltrate containing wellformed granulomas with differentiated macrophages, epithelioid and giant cells, and a predominance of CD4+ T cells at the lesion site, with low or absent bacteria. Patients show a vigorous-specific immune response to M. leprae with a Th1 profile, IFN-γ production, and a positive skin test (lepromin or Mitsuda reaction).

Lepromatous patients present with several skin lesions with a preponderance of CD8+ T cells in situ, absence of granuloma formation, high bacterial load, and a flattened epidermis. The number of bacilli from a newly diagnosed lepromatous patient can reach 1012 bacteria per gram of tissue. Patients with LL leprosy have a CD4 : CD8 ratio of approximately 1 : 2 with a predominant Th2 type response and high titers of anti-M. leprae antibodies. Cell-mediated immunity against M. leprae is either modest or absent, characterized by negative skin test and diminished lymphocyte proliferation[6].

Complications

- Paralysis and crippling of hands and feet.
- Shortening of toes and fingers due to reabsorption.
- Chronic non-healing ulcers on the bottoms of the feet.
- Blindness.
- Loss of eyebrows.
- Nose disfigurement[7].

Signs and symptoms

- Numbness of affected areas of the skin.
- Loss of sensation in a skin lesion.
- Enlarged peripheral nerve.
- Positive skin smears.
- Muscle weakness or paralysis (especially in the hands and feet)
- Enlarged nerves (especially those around the elbow and knee and in the sides of the neck)
- Eye problems that may lead to blindness (when facial nerves are affected) [8].

Diagnosis

The diagnosis ofleprosy remains clinical and easy tomake for health workers used to treat those patients. The biggest challenge isto suspect the diagnosis of leprosy, especially in industrialized countries where the disease has now almost entirely disappeared. Choosing the right lesion that will then be sent for pathological and biological analyses is crucial and requires clinical expertise of leprosy lesions. Paraclinical tests can help confirm the clinical diagnosis of leprosy, i.e. bacteriological and pathological analyses. No other biological analysis can be recommended.

Clinical diagnosis

The clinical analysis of the skin lesions and nerve damage must be performed by an experienced leprosy clinician. The results will help diagnose and classify the patient's disease presentation according to both RJ and WHO classifications, which will then inform the choice of an adequate treatment, determine the patient's infectiousness, and help prevent potential reversal reactions. Microbiological and pathological analyses should be performed whenever possible to support the clinical diagnosis. Such analysesshould preferably be performed using a skin biopsy or a nerve biopsy when the patient is mainly presenting with neuritis sign[9].

Bacteriological diagnosis

Microscopic analysis and acid-fast bacilli

M. leprae cannot be cultured in vitro; researching resistant acid-fast bacilli with an optical microscope remainsthe standard diagnostic technique. Tissue fluid smear tests or biopsy cell suspensions, once crushed and spread out onto the slide, are stained with the Ziehl-Neelsen staining technique. Bacilli take a fuchsia color on a blue background (Fig. 3).

The number of bacilli contained in each microscopic field or bacterial index (BI) is calculated with the Ridley index [43] for skin smears (earlobe and skin lesions). Tuberculoid leprosy is associated with a negativeBIin the tissue fluid ofthe earlobe and a negative or equal to "1+" BI in skin lesions. In lepromatous leprosy, the BI is positive, always > "2" with bacilli grouping togetherto form globi. An initially highBI(≥ "4+")is consistent with a higherrisk oftransmission and relapse.Compliant patients have a decreasing BI, but most patients with a high BI still have a positive BI at the end of the treatment course as the clearance of non-viable residual bacilli can take years.

Molecular techniques

The analysis of the DNA of M. leprae is done with the PCR technology. Several target genes and antigens have been suggested to detect it in smear tests: pra-36 KDa, pra-18 KDa, RLEP, Ag85B, 16S RNA, folP,rpoB, and gyrA. Specialized laboratories perform those analyses on

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the skin lesion biopsies presenting the highest bacilli count as they are associated with the best detection rate.

PCR sensitivity is close to 100% in patients presenting with a positive bacteriological index, but it is significantly lower in patients presenting with a negative bacteriological index. Sensitivity figures vary between studies and methods, ranging from 87% to 100% for lepromatous patients and from 30% to 83% for tuberculoid patients. PCR sensitivity makes it possible to confirm a leprosy diagnosis, highlighting the presence of the DNA of M. leprae in the lesions.

Pathological diagnosis

The biological diagnosis of leprosy must include a pathological analysis of the skin biopsies. Tuberculoid leprosy presents with nodular and histiolymphocytic infiltrations surrounding the adnexa and nerves; an infiltration or even destruction of the nervules and sudoriferous glands can also be observed, leading to the hypoesthesia or anesthesia of the lesions.

Lepromatous infiltrations are dense with histiocytic cells characterized by foamy cytoplasm (Virchow's cells). They usually surround hair, adnexa, and nerves without invading them. They are separated from the superficial part of the dermis by the band of Unna. Infiltrations have no destruction potential and patients do not present with any sensory impairment.

Immunological diagnostic

Infection by M. leprae leads to a cell-mediated humoral response and to the production of non-protective antibodies. One of the antigens of M. leprae, known as phenolic glycolipid-1 (PGL1), was studied for diagnostic test purposes. Several epidemiological studies used a specific serology test to detect anti-PGL1 IgM or a more recently developed test that can detect both anti-PGL1 IgM and anti-LID1 IgG (fusion protein specific to M. leprae). This serology test is neither marketed nor recommended because of its low sensitivity, especially for paucibacillary presentations of leprosy (thus offering a limited added value), and its inadequate specificity for population of patients frequently infected by other tuberculoid and non-tuberculoid mycobacteria[10].

Treatments

Early clinical diagnosis and treatment are instrumental in reducing the transmission of leprosy and preventing the development of severe complications. Before pharmacological therapy, patients have undergone prednisolone challenge or skin biopsy with PCR testing to assess for known genetic markers of drug resistance. This allowed for a more effective treatment plan that ensured a lower probability of treatment failure. Due to the rising risk of bacterial resistance to therapy, like tuberculosis, the treatment options for leprosy consist of a multidrug approach, precisely, a three-drug regimen. According to the guidelines of the National Hansen's Disease Program (NHDP), which is also supported by the World Health Organization (WHO), the first-line medications include Dapsone, Rifampin, and Clofazimine. Treatment alternatives (second line) for patients who failed a first-line anti-leprosy treatment or when drug resistance is detected include Ofloxacin and minocycline.

First-line antibiotics:

dapsone, clofazimine, and rifampicin.

These are the most effective in the treatment of leprosy, but they do carry certain risks. Dapsone contains bacteriostatic activity that inhibits bacterial synthesis of dihydrofolic acid, thereby inhibiting bacterial nucleic acid synthesis and replication. Prior to the imitation of treatment, all patients should be screened for glucose-6-phosphate dehydrogenase deficiency, as dapsone may cause hemolytic anemia in these patients. Other adverse reaction of dapsone includes hypersensitivity syndrome, methemoglobinemia, and agranulocytosis. Moreover, rifampin contains bactericidal activity that inhibits bacterial DNA-dependent RNA polymerase, thereby preventing the elongation of the messenger RNA. The effect impedes RNA synthesis and results in cell death. Some notable drug side effects include Cytochrome P450 activation, hepatotoxicity, drug-induced hepatitis, and thrombocytopenia. In addition to the other agents, clofazimine contains bactericidal and anti-inflammatory activity that binds to mycobacterial DNA, thereby impeding bacterial growth. Some significant drug side effects include red-black skin discoloration, retinopathy, nephrotoxicity, and cardiac arrhythmi.

Second-line agents:

fluoroquinolones, minocycline, and clarithromycin

Fluoroquinolones (ofloxacin, levofloxacin, and moxifloxacin), minocycline, and clarithromycin are intended as potential therapeutic alternatives. These antibiotics have the same broad-spectrum activity as rifampicin and target many Gram-positive and Gram-negative bacteria. They

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can be administered to patients presenting with an intolerance, resistance, or clinical failure to first-line agents. Patients presenting with rifampicin-resistant leprosy need to take those antibiotics daily, and treatment durationmust be extended to 24 months because of a lower bactericidal activity compared with rifampicin[11].

New therapeutic approaches

Very few new agents active against M. leprae are currently being developed. Bedaquiline (diarylquinoline, R207910, or TMC207) is a new tuberculosis treatment that inhibits the ATP synthase.The bactericidal activity of bedaquiline against M. leprae observed in mice issimilarto that of moxifloxacin and rifampicin. Bedaquiline has not yet been tested on leprosy patients.

Table 1: Standard multidrug therapy regimens for paucibacillary and multibacillary leprosy in adults and children

Clinical presentations	Population	Agents	Dosing regimen	Treatment duration
Paucibacillary leprosy	Adults	Rifampicin	600 mg/month	6 months
		Dapsone	100 mg/day	
	Children	Rifampicin	450 mg/month	6 months
		Dapsone	50 mg/day	
Multibacillary leprosy	Adults	Rifampicin	600 mg/month	12 months
		Clofazimine	300 mg/month and 50 mg/day	
		Dapsone	100 mg/day	
	Children	Rifampicin	450 mg/month	12 months
		Clofazimine	150 mg/month and 50 mg/day	
		Dapsone	50 mg/day	

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