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RECENT ADVANCEMENT IN LEPROSY

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ABSTRACT

Since the time of Bible, leprosy has been recognized to be caused by the mycobacterium leprae. It remains prevalent in many parts of the world and affects Brazil's public health. In Brazil, the prevalence rate in 2011 was 1.54 cases per 10,000 people. Leprosy is spread by prolonged intimate contact between genetically predisposed and sensitive people and untreated multibacillary patients. Bacilli seen in upper airway discharge that are inhaled during transmission. The primary entrance or departure point for M. leprae is the nasal mucosa Understanding of the pathogenesis, variations in clinical characteristics, and progression of the disease have been aided by increased knowledge of the structural and biological characteristics of M. leprae, its genome's sequencing, and the mechanisms of host immune response against the bacilli, which are dependent on genetic susceptibility. In this study, etiopathogenic, clinical, and epidemiological aspects of leprosy are updated for dermatologists.

KEYWORDS: Classification, clinical diagnosis, disease transmission, infectious, epidemiology, t-cell response, genetic phenomena, recent advancement in treatment, MDT

INTRODUCTION

The pathogen Mycobacterium leprae, sometimes known as M. Leprosy, commonly known as Hansen's disease, is a persistent, polymorphic, non-fatal infectious disease that is brought on by lepromatosis.1 dermatological, and neurological disorder.2 It is a rod-shaped, acid-fast bacillus.3 This illness has existed for all time.4 The skin and peripheral nerves are the sites it most commonly affects, but it can also affect the eyes, mucous membranes, bones, and testicles. Additionally, it produces a range of clinical characteristics. M. Leprae In the skin, favours keratinocytes, macrophages, and histiocytes. Schwann cells are home to M. leprae in peripheral nerves.5 Based on a patient's skin and neurological evaluation, the condition is diagnosed.6

Beginning as early as 2400 BCE, the illness first appeared in Egypt and other Middle Eastern nations. Leprosy is a global issue, although it is most common in India, Brazil, the Central African Republic, Tanzania, the Democratic Republic of the Congo, and Mozambique.4 Since the early 1990s the prevalence of leprosy has decreased by 90 percent. Thus, whereas millions of cases of the disease were known in the 1980s, newly reported cases dropped to about 763,200 in 2001 and to some 249,000 in 2008. The disease has disappeared from most temperate countries, but it still occurs in Brazil and in some areas of Africa and southern Asia.7 Leprosy rates have decreased over time, although the World Health Organization (WHO) recorded 184,212 patients that were receiving treatment by the end of 2018. A prevalence rate of 0.24 per 10,000 people was recorded in 2019 (WHO). In the same year, the WHO officially reported 208,619 new cases, which corresponds to a new case detection rate of 2.74 per 100,000 people. At the end of 2018, there were 85,302 cases in India overall, and 120,334 new cases had been found (WHO 2019).8

Diagnosis of leprosy thus can be made by the clinical signs alone; however, in absence of definitive cardinal features, confirmation of leprosy can be difficult in some patients especially in a non-endemic country.9 The main difficulties of working with M. leprae are that it cannot be grown in axenic culture and that its doubling time in tissue is slow, nearly 13 days.10

Since 2014, the German Dermatological Academy has provided many Tropical Dermatology CME courses that are module-based each year. These courses, which are offered in Germany and in dermatological clinics in tropical nations, are necessary to get the "Tropical and Travel Dermatology" credential. In both the basic and advanced courses in Germany, students get familiar with the typical tropical dermatoses that both immigrants and visitors with ties to their native countries experience. The identification of a tropical infectious illness is one of the learning objectives, and it will be demonstrated how early and accurate interpretation of dermatological findings may commonly do so. Leprosy has not been thoroughly covered in the aforementioned course series since it is uncommon to come across a patient with it in Germany. The Regional Dermatology Training Center (RDTC) in Moshi or Colombo, Sri Lanka, where course participants visited, for example, have demonstrated this.

Tanzania-that leprosy, as a persistent infectious illness, continues to be crucial to the provision of fundamental dermatological patient treatment. Every dermatologist working in these nations has a difficulty as a result of its clinical variety. In endemic areas, this intricate dermatological and neurological infectious illness continues to be a significant risk factor for severe impairment. The only way to achieve full remission is by early detection of its distinctive skin lesions and the beginning of effective therapy. The current CME article's goal is to draw attention to the different dermatological characteristics as well as neurological indications and symptoms that even dermatologists may be able to notice. Additionally, readers should get familiar with the language used to describe the various clinical phases since they will be required to know it when they attend dermatology treatment center in endemic areas.11

HISTORY

Since the time of the Bible, accounts of leprosy cases have been documented. Whether leprosy originated in Asia or Africa is a matter of debate. The word "leprosy" honours the Norwegian doctor Gerhard Armauer Hansen, who discovered in 1873 that the disease was caused by the bacteria Mycobacterium leprae. 6

Leprosy was most likely a disease that affected human populations in Egypt,12 India and China , In India, the term ‘Kushtha’ occurring in the Vedas has been belived by some workers to relate to leprosy. In china there is no definite reference to the existence of leprosy in the ancient literature of the country, but there is a tradition that a disciple of Confucius died of leprosy about 600 B.C.13 Paleontology and its application of molecular biology allowed for the identification of the first biological evidence of leprosy discovered in humans. A man's skeleton from the first century BC that was discovered in a cemetery not far from Jerusalem had the DNA of M. leprae extracted from its bones. 14

EPIDEMIOLOGY

Leprosy eradication was defined by the World Health Organization (WHO) in the 1990s

as a reduction in prevalence to 1 case per 10,000 people in all endemic countries. This goal was set for the year 2000. With Europe excluded, between 1985 and 2011, the number of cases reported decreased from 5.4 million to 219,075 while the prevalence rate per 10,000 decreased from 21.1 to 0.37. According to the WHO, 202,256 new leprosy cases were recorded globally in 2019; 14,893 of those cases included children under the age of 14. 10,816 of the brand-new patients at the time of diagnosis had grade 2 impairments.15

Brazil is second only to India in terms of the total number of cases, which has achieved its goal of eradicating leprosy as a public health issue (defined as the prevalence lower than 1 case per 10,000 population). Brazil reported 33,955 new cases in 2011, with an infection prevalence rate of 1.54 per 10,000 individuals and 61% multibacillary cases (MB). According to the prevalence rates per 10,000 people, the Midwest has a rate of 3.75, the North has a rate of 3.49, the East has a rate of 2.35, the Southeast has a rate of 0.61, and the South has a rate of 0.44. The prevalence of new cases detected, the prevalence of new cases in children under the age of 15, and the prevalence of patients with a grade 2 handicap are the key epidemiological indicators used in Brazil. 6

Multibacillary leprosy new cases varied from 32.70% in the Comoros Islands in Africa to 95.04% in the Philippines. In newly discovered cases, the percentage of females varied from 6.50% in Ethiopia to 59.11% in the Central African Republic. Children made up between 0.60% of new cases in Argentina and 30.30% in Papua New Guinea. In new instances, the prevalence of grade 2 impairments ranged from 1.45% in Liberia to 22.8% in China. The detrimental effects of the illness on the physical, social, and economic well-being of those with leprosy and their family are anticipated to diminish as the number of new cases diminishes.16

Early diagnosis and rapid treatment of cases are key components of the Ministry of Health's Coordination for Leprosy and Diseases under Elimination's approach to disease control, which aims to eradicate the sources of infection and prevent sequelae. Partnerships and integrated services help to support disease control efforts. 6

DIAGNOSIS17

In countries where people are frequently infected, a person is considered to have leprosy if they have one of the following two signs:

Skin lesion consistent with leprosy and with definite sensory loss.

Positive skin smears.

Lesions on the skin can be isolated or many, hypopigmented in the majority of instances, but infrequently reddish or copper in colour. The lesions could be flat lesions (macules), papules, or solid raised areas (nodular). The presence of sensory loss at the lesion is a feature that can help determine if a skin lesion is brought on by leprosy or another ailment, such as tineaversicolor. Thicker nerves are associated with leprosy, which may also be accompanied by sensory loss or muscular weakness. However, in the absence of the usual skin lesion and sensory loss, muscle weakness is not typically seen as a reliable sign of leprosy.

Although acid-fast leprosy bacilli in skin smears are occasionally regarded as diagnostic, the diagnosis is normally made on the basis of symptoms without the use of laboratory testing. A fresh leprosy diagnosis is deemed late if the patient already exhibits apparent symptoms of the disease.

Leprosy diagnosis is frequently postponed in nations or regions where it is uncommon, like the United States, since healthcare professionals are not familiar with leprosy and its symptoms. The hallmark of leprosy, nerve involvement, and the handicap it produces are prevented by early diagnosis and treatment.

The diagnosis is typically determined on the basis of symptoms without the need of laboratory testing, even though acid-fast leprosy bacilli in skin smears are occasionally considered diagnostic. If the patient already displays obvious indications of the disease, the diagnosis of leprosy is considered to be late.

Leprosy diagnoses are frequently delayed in nations or regions where the disease is uncommon, such as the United States, since medical professionals are not familiar with the disease's signs and symptoms. Early detection and treatment can stop both the leprosy's characteristic nerve involvement and the handicap it produces.

RECENT ADVANCEMENT IN DIAGNOSIS OF LEPROSY

In 2014, the Information, Education, and Communication (IEC) programme and socioeconomic rehabilitation designs made widespread recommendations for leprosy detection methods. IEC claims that various diagnostic techniques were applied, each of which focused on a particular activity area and compared the outcomes to those of other activities.18 T-cell responses were evaluated using recombinant M. lepre. They discovered that a variety of antigens were immunogenic and leprosy-specific. The study's overall finding was that several antigens were promising candidates for use in leprosy diagnosis or maybe vaccination in the future.19 The goal of was to investigate how leprosy is affected by toll-like receptor 2 (TLR-2) responses. Leprosy patients and a group of individuals with a controlled condition were both subjected to analysis of three different forms of polymorphism in TLR-2. The study's findings showed that the 597CT polymorphisms and microsatellites both had an impact on the vulnerability to reverse reaction and its recurrence, and the capacity to contribute new knowledge on leprosy-related immunogenetics.20 discovered the relationship between leprosy and three single nucleotide polymorphisms (SNPs) in the gene for -defensin 1. (DEFB1).

The findings indicated that DEFB1 might be utilized for early identification and as a marker for lepromatous leprosy (L-lep), as well as for the development of new, curative leprosy treatments.21 Using electrophysiological correlation, evaluated the applicability of ulnar nerve sonography in leprosy. Sonography was used to study a total of 21 infected and 20 control individuals, and it was determined that both sonography and electrophysiology were effective for detecting leprosy.22 used peripheral blood mononuclear cells from leprosy-infected individuals to examine the M. leprae antigens for their capacity to trigger cytokine discharges. The analysis of T-cell responses specific to leprosy and healthy close contacts revealed that ML2283- and M. leprae peptides are promising candidates for diagnosis.23 evaluated the polymorphisms of gene encoding ficolin -2 (FCN2) – a soluble pattern recognition molecule. Results showed that the administration of functional FCN2 haplotypes was significantly different for infected and control leprosy subjects. It was concluded that FCN2 plays an immunogenetic role in the host against M. lapre.24 Leprosy diagnosis is based on slit skin smear for long-term Acid Fast Bacilli (AFB) evidence. It is

acknowledged that this treatment has a number of drawbacks, including the fact that AFB is not always visible in patients, particularly those who belong to the paucibacillary group, such as True Tuberculoid (TT) and Borderline Tuberculoid (BT) types. Since demonstrating AFB requires qualified technicians and referral labs, this process is currently only used in academic settings rather than in the real world.

Another step in the diagnosis of leprosy is the histopathological study of biopsy specimens from the skin or nerve, which provides additional details on the type of infiltration and nerve involvement.

PCR based diagnosis of leprosy,

Immunological test for leprosy,

High-Resolution ultrasonoghraphy in leprosy,

Electo-neuromyoghraphy25

TREATMENT PRINCIPLE OF LEPROSY

Several chemotherapy treatments are effective against M. leprae. The foundation of the multidrug treatment (MDT) regimen suggested by the WHO consists of dapsone (diaphenylsulfone, DDS), rifampicin (RFP), clofazimine (CLF, B663), ofloxacin (OFLX), and minocycline (MINO). M. leprae can also be successfully treated with additional chemotherapy drugs including Levofloxacin (LVFX), Sparfloxacin (SPFX), and Clarithromycin (CAM).26,27,28 For both PB and MB leprosy, the WHO has created highly useful kits that include medicine for 28 days that is given out in blister packs. The precise dose for each of the three components of the MDT regimen is included in the blister pack medicine package for SLPB leprosy.

Patients with PB are given 100 mg of dapsone every day for six months along with 600 mg of RFP once a month under supervision. A single therapeutic dosage of 600 mg RFP, 400 mg OFLX, and 100 mg MINO is effective for treating SLPB patients. Treatment for MB patients includes 100 mg dapsone and 50 mg CLF daily for a period of 12 months, as well as 600 mg RFP and 300 mg CLF monthly, under supervision. For youngsters, lower dosages of the aforementioned regimen are set in an acceptable manner.29,30,31

In order to prevent medication resistance, monthly supervised treatment of RFP is crucial. Health professionals should ensure that consistent and daily, uninterrupted medication intake is carried out throughout the additional 27 days of dapsone (and CLF) therapy that is required.

ADVANCEMENT IN TREATMENT OF LEPROSY

Recently, several researchers created a variety of leprosy prevention methods. Moxifloxacin was studied for its efficacy against patients with multiple bacterial leprosy (MB-Leprosy). Almost 82 to 99% of the bacteria were killed by the medicine, and after a further three weeks of therapy, no viable germs were found. Skin lesions and leprosy patients' resolution both improved quickly with little to no negative effects after using this therapy.32 Infecting mice with low and high dosages of Mycobacterium leprae foot pad (FP) infections allowed researchers to compare how lymphotoxin (LT) affected leprosy control. The study provided evidence that the host's genetic susceptibility to leprosy is important.33 undertook a study in 2010 that included 124 PB patients

to compare the effectiveness of a 4-week treatment using ofloxacin with the WHO-mandated multi-drug therapy (WHO- MDT) against leprosy. According to the results, patients who received ofloxacin treatment had a follow-up of 10.8 years, whereas those who received WHO-MDT treatment had a follow-up of 11.3 years, with one relapse occurring in the third year of treatment and two late relapses occurring in the eighth and twelfth years, respectively. With extremely few relapses, both therapies were successful.34 High-resolution ultrasound (HRUS), a technique for leprosy diagnosis, is employed at the primary level.35 In a case study, two leprosy patients were looked at. In the initial clinical examination, symptoms such adenopathy, fever, and basophilia were examined, and an AFB test was used to determine whether a tuberculosis (TB) infection was active. A combination of medications that responded to the symptoms were used to treat it. FoxP3's function in the suppression of leprosy-causing T cells was examined.36 The T and CD4+ CD25+ cells, as well as the CTLA- 4 and CD25 genes that were extracted from BL/LL patients, were inhibited by it, and it also shown significant binding relationships with deacetylase 7/9 and histone acetyl transferase.37 Leprosy and TB are believed to be caused by the T allele. The body's generation of T cells is mostly reduced or inhibited as part of the leprosy treatment. Additionally utilised to prevent leprosy are carriers of the IFNG+874T allele.38

Treatment with platelet-rich plasma (PRP) is widely used to heal chronic wounds. This therapy was applied to 2 individuals with neuropathic leprosy lesions by Conde et al. According to their findings, PRP was effective in treating leprosy.39 administered a novel vaccination to two groups and conducted a double-blind case study on them.

On one group, "Mycobacterium IndicusPranii (MIT)" coupled with multi-drug treatment (MDT), and on the other, MDT with a placebo. The outcomes demonstrated that MDT and MIT were both more effective.40

TREATMENT OF MULTI-DRUGS THERAPY

Rifampicin (RFP): Designed a uniform multi-drug therapy (U-MDT) for all types of leprosy patients using a combination of 3 drugs, clofazimine, depsone and rifanpicin. The aim of study was to observe the effect of U-MDT towards multibacillary (MB) and paucibacillary (PB0 groups. The study concluded that PB patients responde much better than MB patients using U-MDT and it was also a promising therapy for skin lesion leprosy.41 The efficacy of rifampicin for the inhibition of leprosy , in people who weew in close contacts with patients of newly diagnosed leprosy, by using single and double blind, and placebo- controlled trials in Bangladesh. The results concluded that a single dosee of rifampicin was potent against development of leprosy at, two-year stage , for the close contacts of patients.42 Developed a new strategy of using Bacilli Calmette-Guerin (BCG) vaccination in combination with rifampicin for the treatment of leprosy The joint effect of BCG vaccination and rifampicin against leprosy was 80% which concluded that combination therapy could lower the prevalence.43

Diaminodiphenylsulfone (DDS, dapsone): Dapsone, which is either barely bactericidal or bacteriostatic against M. The main component of the leprosy treatment plan was leprae. That is, up to the discovery of widespread drug resistance strains.44 As a result, its use in conjunction with other medicines has increased. It is vital to stop or postpone the development of resistance. When

administered at the dosage used in MDT, the medication has shown to be appropriately safe. With the exception of sporadic cutaneous eruptions, the bulk of unpleasant symptoms need to stop. Dapsone should not be administered to patients who are known to be allergic to any sulpha medication. Patients lacking glucose-6-phosphodihydrogenase are more likely to experience methemoglobinemia, hemolysis, and anaemia (G6PD). 45

Clofazimine (CLF): Clofazimine was used as a leprosy monotherapy from the early 1960s through the middle of the 1970s. Clofazimine is bacteriostatic and slowly bactericidal against M. Leprae, similar to dapsone, but it is unknown how it functions. The drug may function by increasing lysosomal enzyme synthesis, inhibiting DNA from acting as a template, and enhancing macrophage phagocytosis. Despite being delayed to take effect, resistance to clofazimine is highly rare—possibly as a result of its multiple mechanisms of action.

The main side effects of clofazimine are increased skin pigmentation and dryness (ichthyosis), which appear as the drug gets closer to clinical efficacy. In addition, pigmentation is present in the cornea, conjunctiva, and macular areas of the eyes.46

Ofloxacin, pefloxacin, sparfloxacin, temafloxacin, moxifloxacin, and sitafloxacin are fluoroquinolones. This class of medications works by inhibiting DNA gyrase, which thereby prevents DNA coiling and supercoiling. In less than a month of treatment, ofloxacin kills more than 99.99% of viable M. leprae, demonstrating its exceptional efficacy. The bactericidal activity of moxifloxacin is comparable to that of rifampicin.

Mild adverse effects can include headaches, nausea, dizziness, diarrhoea, and sleeplessness. Fluoroquinolones are not utilised in youngsters due to their impact on cartilage formation.47

The fluoroquinolone antibacterial medicine doxifloxacin, which has FDA approval, increases the risk of tendinitis and tendon rupture, especially in people over 60. It is a last-resort medication used when all other antibiotics have failed. In clinical studies for drug-resistant tuberculosis, a single dose of moxifloxacin up to 800 mg was well tolerated, but after six months of continuous 400 mg once day treatment, some patients experienced serious side effects (nausea, vomiting, muscle soreness, tremors, sleeplessness, and dizziness). 48

LEPROSY COMPICATION

Withouttreatment, leprosy can permanently damage your skin, nerves, arms, legs, feet, and eyes. Complications of leprosy can include:

Blindness or glaucoma,

Iritis,

Hairloss

Infertility

Disfiguration of the face (including permanent swelling, bumps, and lumps)

Erectile dysfunction and infertility in men

Kidney failure

Muscle weakness that leads to claw-like hands or a not being able to flex your feet

Permanent damage to the inside of your nose, which can lead to nosebleeds and a chronic stuffy nose49

During their treatment they were seen monthly in the outpatient department by a dermatologist, and every adverse effect, therapeutic decision and classification of leprosy were recorded in their personal record. Hemolytic anemia, leucopenia, methaemoglobinemia and liver abnormalities were confirmed by laboratory examination. All other diagnosis was based on clinical signs and symptoms. Laboratory assessments were done before the start of MDT and on 30th, 60th and 90th days of the treatment. Tests included full blood count and Adverse effects of Multi-drug therapy in leprosy 19 liver function tests. A test for methemoglobin was done only when there was clinical suspicion of Methemoglobinemia like shortness of breath, cyanosis, headache and fatigue etc.50

Table 1:- Recommended doses for leprosy

Diagnosis	Population	Medication	Dose	Duration
Paucibacillary leprosy	Adults	Rifampicin	600 mg/month	6 months
		Clofazimine	300 mg/month + 50 mg/ month	
		Dapsone	100 mg/month	
	Children	Rifampicin	450 mg/month	6 months
		Clofazimine	150 mg/month + 50 mg/month	
		Dapsone	50	

			mg/month	
Multybacillary leprosy	Adults	Rifampicin	600 mg/month	12 months
		Clofazimine	300 mg/month + 50 mg/month	
		Dapsone	100 mg/month	
	Children	Rifampicin	450mg/month	12 months
		Clofazimine	150 mg/month + 50 mg/month	
		Dapsone	50 mg/month	

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