International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR | Volume 9 | Issue 1 | Jan - Mar - 2021
www.ijamscr.com

Review Study Medical research

A brief review on hansen's disease

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ABSTRACT

Hansen disease is also known as Leprosy. Leprosy is caused by Mycobacterium leprae and has been known since biblical times. The mechanism of transmission of leprosy consists of prolonged close contact between susceptible and genetically predisposed individuals and untreated multibacillary patients. Transmission occurs through inhalation of bacilli present in upper airway secretion. The nasal mucosa is the main entry or exit route of M. leprae. The deeper understanding of the structural and biological characteristics of M. leprae, the sequencing of its genome, along with the advances in understanding the mechanisms of host immune response against the bacilli, dependent on genetic susceptibility, have contributed to the understanding of the pathogenesis, variations in the clinical characteristics, and progression of the disease. This article aims update on epidemiological, clinical, and etiopathogenic leprosy aspects.

Keywords: Classification, Clinical diagnosis, Disease transmission, Epidemiology, Leprosy, Mycobacterium leprae

INTRODUCTION

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It is highly contagious, but its morbidity is low because a large portion of the population is naturally resistant to this disease. Leprosy affects mainly the skin and peripheral nerves. Its diagnosis is established based on skin and neurologic examination of the patient. Early diagnosis is very important. The timely and proper implementation of treatment will prevent sequelae and physical disabilities that have an impact on the individual's social and working life, which are also responsible for the stigma and prejudice regarding this disease.

HISTORY

This disease has been known as leprosy since the biblical times, with reports of cases dating over 3000 years ago. There are doubts whether leprosy originated in Asia or Africa. The term Leprosy is a tribute to the Norwegian physician Gerhard Armauer Hansen, who identified the bacillus *Mycobacterium leprae* as the cause of the disease in 1873.[1]

Leprosy is believed to have been introduced in Europe from India by the troops of Alexander, the Great, 300 BC. Its incidence was high in Europe and the Middle East during the Middle Ages. The number of cases was dramatically reduced around 1870 because of the socioeconomic development. Leprosy is assumed to have been introduced in Latin America during the colonization period by French people in the United States and by Spanish and Portuguese people in South America. African slave traffic was the major cause of the spread of leprosy in the Americas. The first cases were reported in Brazil in 1600 in the city of Rio de Janeiro. The first isolation hospital was installed in Rio de Janeiro. After that, the disease spread to the other Brazilian regions. [2]

The main strategy used to prevent the spread of leprosy in the past was the compulsory isolation of patients in leper colonies, which were established in Brazil in 1923. With the introduction of sulfone in the 1940s and its use in the treatment of leprosy due to its effectiveness, isolation was no longer mandatory; however, it was only officially

abolished in 1962. Nevertheless, until the mid-1980s, many patients still remained isolated for several reasons. Because of cases of resistance to sulfone monotherapy in 1970, the World Health Organization (WHO) suggested the use of multidrug regimens. Therefore, since the early 1980s, the disease has been treated with multidrug regimens in outpatient settings and patients are considered cured after treatment. However, multidrug therapy (MDT) was only extensively and officially implemented in Brazil in 1993.[3]

The term hanseniasis was proposed to reduce the stigma associated with the disease in 1967 by Professor Abraão Rotberg. The term was officially adopted in Brazil in 1970, becoming mandatory according to the federal law no. 9010 effective as of March 29, 1995.[4]

EPIDEMIOLOGY

Leprosy is endemic in tropical countries, especially in underdeveloped or developing countries. Its prevalence has decreased markedly since the introduction of MDT in the beginning of the 1980s. However, 105 endemic countries, specifically located in Southeast Asia, in the Americas, Africa, Eastern Pacific and Western Mediterranean, still concentrate a large number of cases. In 2011, 219,075 new cases were detected in the world. In the first quarter of 2012, 181,941 new cases were recorded and there was a prevalence of 0.34 cases per 10,000 inhabitants.[5]

Epidemiological data from some countries, including India, should be interpreted with caution, because the goals of disease elimination were achieved based on some criteria, such as: changes in the definition of case, exclusion of recurrent cases from the prevalence rate, exclusion of cases of treatment dropout from active records, single-dose treatment of paucibacillary (PB) patients, shorter duration of treatment, etc. This caused a sharp drop in the number of new cases reported. [6]

The reduction of cases of leprosy in children under 15 years old is a priority, because this is the main endemic monitoring indicator. Cases in this age group suggest recent transmission with active infection focus and high endemic area, revealing operational deficiency. An analysis of the people the patient had contact with is likely to find the source of the infection, as this source usually is close. The peak detection of cases in people under 15 years old occurred in 2003, when 4,181 cases were detected, resulting in a detection coefficient of 7.98 per 100,000 inhabitants. Thereafter, the rates have been falling; in 2011, 2,420 new cases were detected, resulting in a detection coefficient of 5.22 per 100,000 inhabitants.[7]

The population's lack of knowledge about the disease and the patients' difficulty to have access to specific treatment in some regions contribute to the late diagnosis of leprosy. This may result in physical disability, an indicator used to measure the quality of services. Although the progressive reduction of physical disability in leprosy cases because of the current larger number of early diagnosis in the country, 2,165 cases had grade-2 disability in 2011. A possible explanation for this might be the hidden prevalence of leprosy; that is, a reservoir of undetected cases influenced by epidemiological and operational elements that preserves sources of infection.[8,9]

The strategy used for disease control by the Coordination for leprosy and Diseases under Elimination of the Health Surveillance Secretariat of the Ministry of Health consists in early detection and prompt treatment of cases to eliminate the sources of infection and prevent sequelae. Integrated services and partnerships support the actions for disease control.[9]

ETIOPATHOGENESIS
ETIOLOGIC AGENT

The etiologic agent, *M. leprae*, was identified by Norwegian physician Gerhard Armauer Hansen in 1873. Therefore, it is also called Hansen's bacillus.

TAXONOMY, MORPHOLOGY, STAINING AND BIOLOGICAL CHARACTERISTICS OF M. LEPRAE

M. leprae's *scientific classification is as follows: class* Schizomycetes, *order* Actinomycetales, *family* Mycobacteriaceae, *and genus* Mycobacterium. M. leprae *is a straight or slightly curved rod, with rounded ends, measuring 1.5-8 microns in length by 0.2-0.5 micron in diameter. In smears, it is red stained with fuchsin using the Ziehl-Neelsen (ZN) stain, and because of its high lipid content, it does not get discolored when washed with alcohol and acid, thus showing the characteristics of acid-alcohol-resistant bacil-li (AARB).* M. leprae *is different from other mycobacteria in terms of arrangement, since it is arranged in parallel chains, just like cigarettes in a pack, bound together forming the* globi. *When the Gram staining method is used,* M. leprae *is gram-invisible, appearing as negatively stained images, called ghosts, or as bead-like gram-positive bacilli.*[10]

M. leprae infects mainly macrophages and Schwann cells. It has never been grown in artificial media. Reproduction occurs by binary fission and it grows slowly (about 12-14 days) in the foot pads of mice. The temperature required for survival and proliferation is between 27 ºC and 30 ºC. This explains its higher incidence in surface areas, such as skin, peripheral nerves, testicles, and upper airways, and lower visceral involvement. *M. leprae* remains viable for 9 days in the environment.[11]

ULTRASTRUCTURAL CHARACTERISTICS OF M. LEPRAE

The ultrastructure of *M. leprae* is common in the genus *Mycobacterium.* Electron microscopy has shown that this bacillus has cytoplasm, plasma membrane, cell wall, and capsule. The cytoplasm contains common structures in gram-positive microorganisms. The plasma membrane has a permeable lipid bilayer containing interaction proteins, which are the protein surface antigens. The cell wall attached to the plasma membrane is composed of peptidoglycans bound to branched chain polysaccharides, consisting of arabinogalactans, which support mycolic acids, and lipoarabinomannan (LAM), similarly to other *mycobacteria.* The capsule, the outermost structure, has lipids, especially phthiocerol dimycocerosate and phenolic glycolipid (PGL-1), which has a trisaccharide

bound to lipids by a molecule of phenol. This trisaccharide is antigenically specific for *M. leprae.*[12]

THE GENOME OF M. LEPRAE

The genome of *M. leprae* was sequenced by Cole et al. in 2001. It is circular. Its estimated molecular weight is 2.2 x 109 daltons, with 3,268,203 base pairs (bp) and guanine + cytosine content of 57.8%. When compared to the genome of *Mycobacterium tuberculosis,* which has 4,411,529 bp and guanine + cytosine content of 65.6%, it seems that *M. leprae* underwent reductive evolution, resulting in a smaller genome rich in inactive or entirely deleted genes. It has 2,770 genes, with coding percentage of 49.5%, that is, 1,604 genes encoding proteins (1,439 genes common to *M. leprae* and *M. tuberculosis*) and 1,116 (27%) pseudogenes. The latter are randomly distributed in the genome and may correspond to regulatory sequences or residual gene mutations that become unrecognizable. These characteristics cause significant reduction of metabolic pathways, thus explaining why the bacillus requires specific conditions to grow.[13]

RESERVOIRS OF M. LEPRAE

Human beings are the reservoir of *M. leprae,* but animals, such as armadillos, chimps, and other apes, the soil, water, and some arthropods are natural reported reservoirs.[14]

MECHANISMS OF LEPROSY TRANSMISSION

It is believed that leprosy transmission occurs by close and prolonged contact between a susceptible individual and a bacillus-infected patient through inhalation of the bacilli contained in nasal secretion or *Flügge* droplets. The main route of transmission is the nasal mucosa.[15]Less commonly, transmission can occur by skin erosions. Other transmission routes, such as blood, vertical transmission, breast milk, and insect bites, are also possible.[16]

It is assumed that infected individuals, even those who did not develop the disease, may have a transitional period of nasal release of bacilli. [17]The presence of specific DNA sequences *M. leprae* in *swabs* or nasal biopsies and seropositivity for specific bacillus antigens in healthy individuals living in endemic areas suggest the carrier plays a role in the transmission of leprosy.[18]

GENETIC FACTORS

Although the exact genes involved in leprosy are not known, it is accepted that different sets of genes of the human leukocyte antigen system (HLA) and non-HLA have an impact on the susceptibility to leprosy, both in infection per se control and in the definition of the clinical presentation. Changes in candidate genes, that is, genes whose product participates in the host response to the infectious agent, have been currently investigated. Genomic scan studies identified binding peaks for leprosy in chromosome regions 6p21, 17q22, 20p13, and 10p13.[19]

MRC1 gene markers located in the 10p13 region are associated with leprosy per se.[19] Analysis of the polymorphisms of exon 7 of the *MRC1* gene, which encodes receptors expressed in macrophages and dendritic cells and are involved in innate immune responses, showed that the G396-A399-F407 haplotype is associated with leprosy per se and the multibacillary (MB) forms. [19] Variations in the *PARK2 and PARCRG* genes are also associated with the control of susceptibility to leprosy per se because they change the response of the macrophages to *M. leprae.* The LTA+80 single nucleotide polymorphism is related to increased risk of leprosy in young populations because it reduces the expression of lymphotoxin alpha (LTA), a cytokine of the tumour necrosis factor (TNF) superfamily that participates in the activation of lymphocytes and is encoded by the LTA gene. [20] Polymorphisms in the promoters of the genes for tumour necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) are associated with the development of leprosy, particularly MB disease, in the polymorphism in the promoter for TNF-α. [21]Analyses using single nucleotide polymorphisms located in the promoter region of the IL-10 gene revealed that the -819T allele is associated with susceptibility to leprosy.Conversely, it seems that the -308A allele of the promoter region of the TNF gene promotes protection against leprosy per se. in addition to regulating TNF production during reactions, with a higher frequency of neuritis in heterozygous patients.[22] Recently, an association genome scan *(Genome-Wide Association)* for leprosy conducted in a Chinese population identified variations in seven genes *(CCDC122, CD13orf31, NOD2, TNFSF15, HLA-DR, RIPK2,* and *LRRK2)* associated with susceptibility to leprosy, with clearer findings for the *CD13orf31, NOD2, RIPK2,* and *LRRK2* genes and MB leprosy.[23]Currently, studies have tried to understand the binding effect observed between the chromosomal region 6q25-q27 and leprosy per se.

Polymorphisms in the promoter genes for TNFα and in the macrophage protein 1 associated with natural resistance (Nramp1) are associated with the development of MB leprosy. Evidence of association between chromosome region 10p13 and paucibacillary (PB) leprosy have been found. This finding has not been confirmed in later studies. Different alleles of the vitamin D receptor *(VDR)* gene are associated with tuberculoid and lepromatous leprosy.[24] In the HLA complex region, there are links with genes of class II antigens, such as HLA DR2 and DR3 alleles associated with the tuberculoid form, and HLA DQ1 allele associated with the lepromatous form.

Variations in the *TLR1* and *TLR2* genes seem to be associated with the reversal reaction. No association has been demonstrated with the occurrence of neuritis or ENH.[25]

IMMUNOPATHOLOGY

A wide variety of clinical and histopathological manifestations of leprosy occurs due to the ability of the host to develop different degrees of cellular immune response to *M. leprae,* which led to the spectral concept of the disease.[26]

The first barrier to infection with *M. leprae* is innate immunity, represented by the integrity of epithelia, secretions, and surface immunoglobulin A (IgA). In addition, natural killer (NK) cells, cytotoxic T lymphocytes, and activated macrophages can destroy bacilli, regardless of

the activation of adaptive immunity. Effective innate immune response modulated by dendritic antigen-presenting cells, in combination with the low virulence of *M. leprae,* can be the basis for resistance to the development of clinical manifestations of leprosy. After the infection is installed, the host immune response is still indefinite in the initial phase. Regulation of inflammatory cytokines and chemokines may lead to proliferation of T *helper* 1 (Th1) or T *helper* 2 (Th2) lymphocytes, which will promote cellular or humoral immune response to *M. leprae*, respectively. This will determine the evolution of the disease to the tuberculoid or lepromatous form.[27]

In addition to being ineffective to prevent the development of the disease, the cellular immunity of the individuals who develop the tuberculoid form of the disease is exacerbated, being directly involved in the onset of skin lesions. The humoral immunity of the individuals who develop the lepromatous form of the disease, which is responsible for the production of IgM antibodies against PGL-1, does not offer protection, allowing bacillary dissemination.[28]

The *in situ* investigation of the phenotype of T lymphocytes using immunohistochemical techniques with monoclonal antibodies demonstrates a predominance of T *helper* (CD4+) in tuberculoid lesions, showing a CD4:CD8 ratio of 2:1, the same ratio found in blood, but with a memory:naive T cell ratio of 1:1 in the blood and 14:1 in the lesions; that is, CD4+ cells in tuberculoid lesions express the phenotype memory-T cells (CD45R0+). In lepromatous lesions, there is a predominance of the population of T CD8+ lymphocytes with CD4:CD8 ration of 0.6:1, regardless of blood ratio. In this lesions, half of the CD4+ cells belong to the subclass of T-naive cells, most CD8+ cells belong to the CD28- phenotype, suggesting that they are T-suppressor cells, whereas T-cytotoxic cells (CD28+) predominates in tuberculoid lesions.It has been observed that CD4+ cells (T memory phenotype) are bound to macrophages in the center of the tuberculoid granuloma and CD8+ cells are the cuff surrounding it. [29] In the lepromatous granulomas, the CD8+ cells (T suppressor phenotype) are mixed with macrophages and CD4+ cells.[30]

The analysis of T cell clones of the lesions shows that different patterns of cytokines are produced by CD4+ and CD8+ subclasses. Clones of CD4+ cells from tuberculoid patients produce high levels of interferon-gamma (IFN-γ), interleukin-2 (IL-2), and TNF-α.[31] These clones were called T CD4+ cells, Th1 pattern, enhancers of cell-mediated immunity and reduced proliferation of *M. leprae.* Clones of CD8+ cells from lepromatous patients produce high levels of suppressor cytokines of macrophage activity, interleukin-4 (IL-4), interleukin-5 (IL-5), and IL-10, as well as low levels of IFN-γ. Considering the pattern of cytokine secretion of T suppressor cells, particularly IL-4, these cell clones have been called T CD8+ cells, Th2 pattern, which contribute to the stimulation of B lymphocytes, with increased humoral immune response and production of antibodies, making the individual susceptible to disease development.[27]

The levels of TNF-α are higher in the serum of tuberculoid patients, suggesting that the destruction of *M. leprae* and the formation of granuloma are associated with the presence of this cytokine. In spite of being involved in defense by means of macrophage activation if produced at high levels and associated with high levels of IFN-γ, TNF-α contributes to tissue damage and symptoms of erythema nodosum leprosum (ENL).[31]

In the lepromatous form, there is elevated transforming growth factor-beta (TGF-β), which is absent in the tuberculoid form and appears in decreasing levels in borderline leprosy. This cytokine suppresses macrophage activation that inhibits the production of TNF-α and IFN-γ which contributes to perpetuate the infection.[32]

Furthermore, IL-7 and IL-12 are growth and differentiation factors of T cells, and they are produced in tuberculoid lesions.[33]Conversely, IL-13 seems to play a role in the immunosuppression of lepromatous lesions.[34]

In type 1 reaction, there is sudden increase in cellular immune response, with influx of T CD4+ cells and production of IL-1, TNF-α, IL-2, and IFN-γ in the lesions, Th1 response pattern. In ENL, there is inflammatory reaction mediated by immune complexes, characterized by increased IL-6, IL-8, and IL-10 in the lesions, suggesting Th2 response , as well as increased TNF-α and TGF-β.[35]

CLASSIFICATION OF CLINICAL FORMS

Several classifications have been proposed for leprosy over the years as new knowledge about the disease was gained. The Madrid classification, established in the International Leprosy Congress, held in Madrid in 1953, follows the polar system defined in 1936 by Rabello Jr. [36]This system is based on clinical characteristics and the result of skin smears, dividing leprosy into two immunologically unstable groups (indeterminate and borderline) and two stable polar types (tuberculoid and lepromatous).

The classification system of Ridley & Jopling (1962,1966) uses the concept of spectral leprosy based on clinical, immunological, and histopathological criteria. [37] The tuberculoid (TT) form is at one end of the spectrum and the lepromatous (LL) form is at the other end. The borderline form is divided into borderline-tuberculoid (BT), borderline-lepromatous (BL), according to the greater proximity to one of the poles, and borderline-borderline (BB).

In 1982, the WHO, with operational and therapeutic purposes, established a simplified classification based on the bacterial index (BI). According to this classification, leprosy was divided into paucibacillary (PB) and multibacillary (MB), and PB patients are those who have a BI lower than 2+ and MB patients are those showing a BI higher than or equal to 2+. [38]In 1988, the WHO recommended the use of a purely clinical classification because there are regions where microscopy examination of skin smear is unavailable, establishing as PB cases those patients with up to five skin lesions and/or only one nerve trunk involved, whereas MB cases are those with more than five skin lesions and/or more than one nerve trunk involved.[39] However, when microscopy examination of skin smear is available, patients with positive results are considered MB, regardless of the number of lesions. Thus, indeterminate, TT and BT patients are included in the PB group. The MB group includes BB, BL, LL and some BT patients.

The combination of the classification by number of lesions with the serological test of lateral flow of *M. leprae (ML-Flow* test), which correlates the BI and the concentration of anti-trisaccharide IgM of PGL-1 in the peripheral blood of patients is an evolution of the operational classification.

Seropositive patients are classified as MB and seronegative patients are considered PB.[40]

CLINICAL MANIFESTATIONS CHARACTERISTICS OF CLINICAL FORMS

Clinical manifestations depend more on the cellular immune response of the host to *M. leprae* than on the bacillary penetration and multiplication ability. Clinical manifestations are preceded by a long incubation period, between six months and 20 years (mean period of two to four years). Seropositivity to antigens of *M. leprae* has been found nine years before clinical diagnosis.[41] Slow proliferation, low antigenicity and metabolic limitation of *M. leprae* are possible explanations for the long incubation periods of leprosy.Decreased sensitivity in the lesions, changing sequentially thermal, painful, and tactile sensitivity are typical manifestations.

The indeterminate group is characterized by a small number of hypochromic spots, with slight decrease in sensitivity, without increased nerve thickness (Figure 1).



(Figure 1)Indeterminate leprosy: Hypochromic spots with indefinite borders on the face

In the TT form, the disease is limited due to the good cellular immune response of the host to *M. leprae,* with the patients showing single skin lesions or a small number of asymmetric lesions. They are characterized by erythematous plaques, often with elevated external borders and hypochromic center, presenting significant change in sensitivity. The lesions may have alopecia and anhidrosis because of denervation of the skin appendages, and thickening of the nearby nerve sheath, and hyperkeratosis and/or ulceration in the compression areas. Sensitive change in the nerve path, with or without clear thickening, may be the only manifestation, characterizing the primary neural form of the disease.



(Figure 2).Tuberculoid leprosy: well-defined annular erythematous plaque on the dorsum of the hand

In the LL form, *M. leprae* multiplies and spreads through the blood because of the absence of cellular immune response to the bacillus. Antibodies are produced, but they do not prevent bacterial proliferation. Skin lesions tend to be multiple and symmetrical, preferably located in the colder areas of the body, characterized by hypochromic, erythematous or bright brownish spots with indefinite borders. These spots may not have loss of sensation. Sometimes, the only noticeable sign is dry skin. Multiple peripheral nerves are compromised, but there is no thickening, unless the patient develops the borderline form of the disease. As the disease progresses, lesions infiltrate forming plaques and nodules (lepromas). Edema in the legs and feet and hypoesthesia of the limbs are other common symptoms. In the advanced stages of the disease, the patient's face has a peculiar appearance (leonine facies), characterized by diffuse infiltration and eyelash loss (madarosis). Mucous membranes, eyes, bones, joints, lymph nodes, blood vessels, upper airways, teeth, and internal organs may be affected



(Figure 3)Lepromatous leprosy: dry and barely discernible hypochromic spots on the arm



(Figure 4)Lepromatous leprosy: ichthyosiform appearance of the skin of the legs and lepromas



(Figure 5)Lepromatous leprosy: infiltrated face and madarosis

The borderline group has different clinical manifestations because of varying degrees of cellular immune response to *M. leprae*. The skin lesions of the BT subgroup resemble the TT form in terms of appearance and loss of sensitivity, but they occur in a larger number and are smaller. Nerve thickening tends to be irregular, less intense, and appears in a larger number. The skin lesions of the BB subgroup exhibit characteristics of the TT and LL forms, with asymmetrical distribution and moderate nerve impairment. The presence of erythematous plaques with fading outer borders, clear inner borders, and hypopigmented oval centre (foveal spot) is suggestive of the BB subgroup. The skin lesions of the BL subgroup resemble the LL form, tending to occur in a large number, but not so symmetrical and with loss of sensation in some areas.

REACTIONAL STATES

Leprosy reactions result from changes in the immune balance between the host and *M. leprae*. Such reactions are acute episodes that primarily affect the skin and nerves, being the main cause of morbidity and neurological disability. They may occur during the natural course of the

disease, throughout treatment or after it. They are classified into two types: type 1 reaction and type 2 reaction.

Type 1 reaction is a result of delayed hypersensitivity and it occurs in borderline patients. These reactions are related to the cellular immune response against mycobacterial antigens and can cause improvement (reversal reaction, pseudo-exacerbation reaction, or ascending reaction) or worsening (degradation reaction or descending reaction) of the disease. Because of the reduction of bacterial load, borderline patients under treatment migrate to the TT pole of the spectrum. Untreated patients show increased bacterial load and the clinical presentation become similar to those of the LL pole because of the deterioration of the cellular immunity. These individuals are classified as subpolar lepromatous. In both cases, the lesions are characterized by hyperesthesia, erythema, and oedema, with subsequent scaling and sometimes ulceration. Lesions are usually combined with oedema of the extremities and neuritis, with minimal systemic manifestations in reactional individuals close to the TT pole and systemic manifestations in those close to the LL pole[(42)]

Type 2 reaction or ENL is related to humoral immunity and does not mean immunological improvement. It is believed to represent the body's reaction to substances released by the destroyed bacilli, with deposition of immune complexes in the tissues. It is manifested by sudden worsening, especially during treatment in the LL individuals and, more rarely, in BL patients. Symmetrically distributed subcutaneous inflammatory nodules or target lesions of erythema multiforme occur in any region. There are general symptoms, such as fever, malaise, myalgia, edema, arthralgia, and lymphadenomegaly. Neuritis and internal involvement, such as liver or kidney damage, may also occur. 43 Inflammatory laboratory tests show abnormal results. There may be necrosis because of obliteration of the vascular lumen (necrotic ENL), probably due to vasculitis with leukocytoclasia due to deposition of immune complexes within vessel walls, with formation of thrombi and ischemia. This should not be confused with Lucio's phenomenon, which occurs in Lucio's leprosy and classic lepromatous leprosy, where a large amount of bacilli infect the capillary endothelium leading to endothelial proliferation, thrombosis, and vascular occlusion.

NEUROLOGICAL CHANGES

In addition to the involvement of dermal free nerve endings, which leads to changes in the sensitivity of skin lesions, *M. leprae* may invade peripheral nerve trunks and cause neuritis. Such lesions develop slowly, with variable pain symptoms, and may cause functional changes. There are exacerbations during the reactions, but they may be silent; in which case, there are functional changes with no pain.[(44)]

Peripheral neuropathy of leprosy is mixed (sensory, motor, and autonomic), and its pattern is that of mononeuropathy or multiple mononeuropathy. Nerves may become thickened, irregular, and painful on palpation. Hypoesthesia or anaesthesia, paresis or paralysis, decreased muscle strength, amyotrophy, tendon retraction, joint stiffness, vasomotor dysfunction, decreased sebaceous and sweat gland secretions may occur with disease progression.These neurological damage contribute to the frequent occurrence of lesions, especially on the hands, feet, and eyes, with occurrence of skin dryness, fissures, and ulcerations, secondary infection in the bone and soft tissues, and bone resorption, causing deformities.[(44)] Neuritis often cause sequelae and may lead to chronic pain along the affected nerves, which is called neuropathic pain.

The most commonly affected nerves are: the facial (7th cranial) and trigeminal (5th cranial) nerves in the face; the ulnar, median, and radial nerves in the upper limbs; and the common fibular and posterior tibial nerves in the lower limbs.

FACIAL NERVE LESION

Facial nerve lesion leads mainly to decreased muscle strength of the eyes and nasal and ocular dryness. The lesion of the zygomatic branch produces orbicularis paralysis and lagophthalmos with or without ectropion. The lesion of the ophthalmic branch of the trigeminal nerve mainly causes decreased sensitivity of the nose and cornea. These changes predispose to keratitis, ulcer, infection, and blindness. The destruction of the fibres of the autonomic nervous system in the nose cause atrophic rhinitis with reduced nasal mucus and decreased blood supply; thus the mucosa becomes pale and fragile with thinned cartilage, which sometimes collapse.[(45)]

NERVE LESION OF THE UPPER LIMBS

Ulnar nerve lesion causes hypoesthesia or anaesthesia, as well as sweating and circulation disorders of the inner edge of the hand and the 4th and 5th fingers, with paralysis and hypotrophy of most intrinsic muscles of the hand, resulting in claw deformity, characterized by hyperextension of the metacarpophalangeal joints and flexion of the interphalangeal joints, especially of the 4th and 5th fingers. This lesion may cause hypothenar and thenar atrophy, as well as atrophy of the interosseous spaces. The little finger becomes abducted and thumb adduction is impaired. Median nerve lesion causes paralysis and atrophy of some muscles of the thenar eminence and loss of palmar sensitivity in the thumb, index, and middle fingers, as well as in the radial and volar half of the ring finger. When muscles are affected at the wrist, there is loss of thumb opponency and hyperextension of the metacarpophalangeal joints of the 2nd and 3rd fingers (claw). When the lesion occurs at a more proximal level, the extrinsic muscles are also compromised, with loss of control of the distal phalanx flexion of the index and middle fingers, loss of function of superficial flexors, pronation impairment, and tendency to ulnar deviation of the wrist. These symptoms make it difficult to handle small objects and to grasp larger objects. Radial nerve lesion is rare, occurring only after the involvement of the ulnar and median nerves (triple paralysis); it is detected by the flexion position (dropwrist) due to the paralysis of the extensor muscles of the wrist, fingers and thumb, making it difficult to grasp objects due to inability to position the hand to hold them, in addition to the atrophy of the dorsal region of the forearm. Sensitivity is impaired in the dorsal aspect of the thumb to the third finger and in the radial portion of the fourth finger.[(45)]

NERVE LESION OF THE LOWER LIMBS

The common fibular nerve may be injured in its superficial and deep branches. Deep fibular nerve lesion leads to changes in the sensitivity of the region above the first metatarsal space, as well as paralysis of ankle and toes dorsiflexion. Superficial fibular nerve lesion leads to loss of sensitivity across the lateral and dorsal surface of the leg and change in the movements of eversion of the foot (remaining in plantar flexion), side of the leg, and dorsum of the foot. When both branches are affected, there is foot drop and atrophy of the lateral and anterior parts of the leg. Posterior tibial nerve lesion causes plantar anaesthesia and paralysis of the intrinsic muscles of the foot, with hyperextension of the metatarsophalangeal joints and flexion of the proximal and distal interphalangeal joints (claw toes), in addition to atrophy of the plantar muscles.[45]

SYSTEMIC CHANGES

Leprosy may affect multiple organ systems, most often in MB patients, particularly in lepromatous, often causing no symptoms. Such involvement may be caused by bacteremia with *M. leprae,* but, most often, the reactional states are responsible for this health impairment. Secondary amyloidosis in several organs is another common cause of kidney damage, and it is associated with the prolonged course of leprosy with recurrent reactional states. Concomitant diseases, side effects of drug treatment, etc, are other possible contributing factors.[46]

RESPIRATORY SYSTEM

M. leprae affects the upper airways (nose, pharynx, larynx, epiglottis, trachea), especially in type 2 reactions. Involvement of the oral mucosa is not frequent.Bronchi are occasionally affected and lungs are usually spared. The association of leprosy and pulmonary tuberculosis is often reported.[47]

CARDIOVASCULAR SYSTEM

arrhythmias, dyspnoea, signs of stasis, ventricular hypertrophy and ST-segment changes are reported more frequently in MB patients than in PB patients. Autonomic dysfunctions are caused by the infiltration of the sympathetic and parasympathetic cardiac nerves. Coronary disease and arteriographic abnormalities of peripheral vessels are reported at a frequency of 11% and 50% of patients, respectively. Infected endothelial cells contribute to the formation of ischemic ulcers. [47]

KIDNEYS AND URINARY PATHWAYS

the involvement of the kidneys is usually due to type 2 reaction or secondary amyloidosis, because *M. leprae* rarely affects the renal parenchyma. There may be glomerulonephritis, interstitial nephritis, nephrotic syndrome, pyelonephritis, acute tubular necrosis, leading to renal failure and death. Ureters, bladder, and urethra are usually spared.[47]

ENDOCRINE SYSTEM

there is significant endocrine involvement, especially in male patients, who have an incidence of up to 90% of testicular involvement, resulting from orchitis, which, with the involvement of the epididymis, can lead to infertility, sexual impotence, and gynecomastia, among other symptoms. Adrenal lesions are reported in about one third of the patients, mainly in the cortex. Inadequate response to stress due to frequent use of corticosteroids in the reactions is a possible event. Thyroid, parathyroid, pituitary and pineal glands are rarely affected. The involvement of the liver by *M. leprae* can occur in all clinical forms of the disease, but is more common in the lepromatous form. It usually is asymptomatic, showing normal liver function tests. When there are abnormal results, other possible causes of dysfunction should be investigated, especially reactions. Secondary hepatic amyloidosis is associates with hepatomegaly.[47]

HEMATOLOGIC AND LYMPHATIC SYSTEM

Bacillemia is present in 90% of lepromatous patients. Bacilli-laden reticuloendothelial cells are frequent in the liver, spleen, and bone marrow. Bone marrow infiltration can cause pancytopenia. There may be surface lymphadenopathy in all skin draining ganglion chains. The iliac, femoral, and paraaortic lymph nodes, as well as those belonging to the portal system, are among the deep and internal lymph nodes affected.

The gastrointestinal tract and female reproductive system are almost always spared. There are reports of low birth weight newborns; pregnancy and lactation predispose to reactions worsening, and recurrence of the disease. The central nervous system is also spared; however, as previously mentioned, involvement of the peripheral nervous system is a classic manifestation.[47]

DIFFERENTIAL DIAGNOSIS

The list of differential diagnosis of leprosy is extremely complex because of the variety of clinical manifestations. The indeterminate form must be differentiated from hypochromic lesions or even achromic lesions, such as pityriasis alba, pityriasis versicolor, hypochromic nevus, post-inflammatory hypopigmentation, and vitiligo. Tuberculoid and borderline lesions may be confused with granuloma annulare, figurative erythema, infectious sarcoid lesions or sarcoidosis, pityriasis rosea, psoriasis, lupus erythematosus, drug eruptions, among others. The lepromatous form may resemble scleroderma, mycosis fungoides, pellagra, asteatosis, ichthyosis, and eczema; multibacillary lesions must be distinguished from secondary and tertiary syphilis, diffuse leishmaniasis, neurofibromatosis, xanthomas, lymphomas, and other tumours. In those case that start with ENL or erythema multiforme, other etiologies should be investigated. The primary neural forms resemble the diseases that cause mononeuropathy or multiple mononeuropathy, including inflammatory, metabolic, infectious, congenital or hereditary diseases, tumours, and traumas. When there are

specific systemic manifestations in multibacillary leprosy, it is important to rule out any diseases that may also cause such manifestations, including systemic lupus erythematosus, rheumatoid arthritis, dermatopolymyositis, and systemic vasculitis. The differential diagnosis of lesions of the nerve trunks of the limbs must be established based on lesions caused by trauma, infection, bleeding, degeneration, and tumours in these nerve trunks that can also cause amyotrophy and paralysis.

TREATMENT

The emergence of drug resistance is the main cause for concern in leprosy because limited number of drugs are available for treatment. Usually, a combination of more than two drugs, with different mechanisms of action, taken regularly for a sufficient period, will prevent the emergence of drug resistance. Resistance to rifampicin, dapsone, and quinolones is reported due to mutations in the binding sites of these drugs in large number of samples by molecular biological methods. Clofazimine and minocycline resistance have not yet been reported. Development of resistance to first-line drugs is becoming serious threat to the efficacy of existing multidrug therapy (MDT) program. Patients suspected to be rifampicin resistant are also expected to be resistant to dapsone. In the year 1998 WHO, technical advisory committee recommended the following regimen for adults with suspected rifampicin resistance.

1. Daily administration of 50 mg of clofazimine, together with 400 mg ofloxacin and 100 mg of minocycline for 6 months, followed by
2. Daily administration of 50 mg clofazimine, together with 100 mg of minocycline or 400 mg of ofloxacin, for at least an additional 18 months.

Newer drug regimens suggested for leprosy in 2009 by the "WHO Report of the Global ProgramManagers' Meeting on Leprosy Control Strategy"

For rifampicin susceptible MB patients, a fully supervised monthly regimen could include Rifapentine 900 mg (or rifampicin 600 mg), moxifloxacin 400 mg, and clarithromycin 1000 mg (or minocycline 200 mg) for 12 months. For rifampicin-resistant patients, the intensive phase could include moxifloxacin 400 mg, clofazimine 50 mg, clarithromycin 500 mg, and minocycline 100 mg daily supervised for 6 months. The continuation phase could comprise moxifloxacin 400 mg, clarithromycin 1000 mg, and minocycline 200 mg once monthly, supervised for an additional 18 months.

A single-dose combination of rifapentine, moxifloxacin, and minocycline killed 99.9% of the viable *Mycobacterium leprae* and was more bactericidal than a single dose of rifampicin, ofloxacin, and minocycline or rifampicin alone. In the same study, it was also observed that the combination of moxifloxacin-minocycline was more bactericidal than the combination of ofloxacin-minocycline.

These drugs such as ofloxacin, moxifloxacin (quinolone), and minocycline are contradicted in children. No alternate regimens are designed for children.

DRUG REACTIONS

In cases of severe adverse reactions, an alternative multidrug therapy regimen is recommended.In adults, the alternative regimens use ofloxacin (quinolone) and minocycline (tetracycline), which are contraindicated in children under 10 years of age, due to the risk of the early closure of the epiphysis as well as dental and bone alterations, respectively.

CONCLUSION

In summary, the incidence leprosy still high in various states of India. Diagnosis of leprosy in children is difficult compared to adults. Incase of doubt, it is better to keep the child under observation for few months, however, in endemic areas, it is always wise to treat the cases at the earliest. The parents should be warned regarding the signs of both types of lepra reaction, so that the treatment can be instituted to avoid deformities due to nerve damage in type 1 reaction and systemic complication in type 2 reactions. All the family members should be examined for evidence of leprosy and treated

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How to cite this article: Dr. R. Manivannan, Dr. S. Kameshwaran, V. Sri Vidhya, S. Divyadarshini and M Uma bharathi. A brief review on hansen's disease. Int J of Allied Med Sci and Clin Res 2021; 9(2): 120-130.

Source of Support: Nil. **Conflict of Interest:** None declared.