American Journal of Infectious Diseases and Microbiology, 2020, Vol. 8, No. 3, 88-94
Available online at http://pubs.sciepub.com/ajidm/8/3/1
Published by Science and Education Publishing
DOI:10.12691/ajidm-8-3-1

Leprosy: A Review of History, Clinical Presentation and Treatments

Kashini Andrew[1,*], Mivanyi Kadala[2]

[1]Stroke Medicine, Morriston Hospital, Swansea, Wales
[2]General Medicine, Northern General Hospital, Sheffield, England
*Corresponding author: kashiniandrew12@gmail.com

Received July 13, 2020; Revised August 15, 2020; Accepted August 24, 2020

Abstract Leprosy is an ancient disease of mankind that has persisted for generations across various continents. The disease is caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis* with humans acting as the natural reservoir. The transmission of Leprosy is still poorly understood, however it is widely accepted that the inhalation of aerosol droplets from cases with high mycobacterial loads is the most common mechanism. Leprosy affects the skin and peripheral nerves and has been a focus of a worldwide eradication campaign by the World Health Organisation which has been largely successful. Treatment is with the use of a multi drug therapy with Dapsone, Rifampicin and Clofazamin for 6 to 12 months depending on the type of leprosy.

Keywords: *leprosy, Mycobacterium leprae, Mycobacterium lepromatosis*

Cite This Article: Kashini Andrew, and Mivanyi Kadala, "Leprosy: A Review of History, Clinical Presentation and Treatments." *American Journal of Infectious Diseases and Microbiology*, vol. 8, no. 3 (2020): 88-94. doi: 10.12691/ajidm-8-3-1.

1. History of Leprosy

References to the history of leprosy in medical literature are extensive, with mentions of the disease in a staggering number of articles and texts. Dr Olaf Skinsnes in his "Notes from the history of leprosy" refers to having come across 18,000 references on the subject in preparing his work. The history of the disease is certainly an interesting and extensive one, stretching back millennia, with evidence for the disease's history present in the form of written documents and palaeontological samples from different locations [1,2]. Understanding the history of leprosy has been useful not only in obtaining a better understanding of the disease itself, but also in dealing with the socio-cultural impact of the fear, misunderstanding and stigma it frequently inspires. The severe deformities and disfigurement associated with the disease has led to revulsion and ostracization of victims of Leprosy throughout history and across cultures. In fact, several cultures including Jewish, Japanese and Chinese associated the disease with sin and personal guilt [3].

The exact origin of leprosy remains uncertain but studies using comparative genomics have ascertained the origin of leprosy to most likely be in East Africa or the near east. From these origins, it is theorised that the disease spread following humans along their migration routes in goods and slave trade. [4] Ancient writings report evidence of leprosy at various times in history in India, China and the middle east, prominent amongst which include the Sushruta Samhita; 600 BC which is widely believed to provide the first clear written description of the disease. [2] Leprosy is thought to have been spread in Europe by Roman invasion and possibly by the crusaders as well, being apparently quite prevalent between 1000 and 1400 AD with proliferation of leper colonies also called Lazar houses. The spread of the disease in the western hemisphere has been attributed to the sailors of Columbus and subsequently, slaves from west Africa. In addition to documentary evidence, there has also been palaeontological evidence. Leprosy is associated with specific erosion of the anterior nasal spine and the alveolar process of the maxilla and palaeopathological studies of ancient skeletal remains have traced leprosy in India to 2000 B.C. [6]

The 19th and 20th centuries saw breakthroughs, with the discovery of the causative organism of leprosy through the visionary work of Armauer Hansen being chief amongst them. It is generally believed that Hansen observed the leprosy bacillus in 1873 and documented this in a communication to the Norwegian Medical Society, which was published in 1874. [7] Thus, Hansen became the first to suggest that a specific microbe caused a chronic disease. Three other significant achievements in the history of leprosy include initial use of sulfone therapy by Dr. Guy Faget of Carville in 1941; discovery that the mouse footpad supported the multiplication of M. leprae by Dr. Charles Shepard of the Centre for Disease Control in 1959; and the demonstration that the nine-banded Armadillo is highly susceptible to developing disseminated Hansen's disease after inoculation with the M. leprae by Dr. Waldemar Kirchheimer of Carville and Dr. Eleanor Storrs of the Gulf South Research Institute in 1968. [6]

In the 1960s, rifampicin and clofazimine were discovered and added to the treatment regimen labelled as Multi-drug

therapy and recommended by the WHO in 1981. Elimination of leprosy as a public health problem (defined as a registered prevalence of less than 1 case per 10 000 population) was achieved globally in 2000. More than 16 million leprosy patients have been treated with MDT over the past 20 years [8]. This in no way makes this an affliction of the past as the most recent WHO figures show that in 2018, 208 613 new cases of leprosy were detected, and the registered prevalence was 184 194 cases, emphasizing the importance of the WHO *"Global Leprosy Strategy 2016-2020: Accelerating towards a leprosy-free world"* to reinvigorate efforts for leprosy control, which focuses on children as well as on avoiding disabilities [9].

2. Epidemiology of Leprosy

The introduction of Multi Drug Therapy (MDT) worldwide in 1982 by the World Health Organisation in response to rising number of dapsone-resistant cases of leprosy was monumental in reducing the number of new leprosy cases worldwide from 5.4 million in the early 1980s to 0.21 million cases in 2014 [9]. The efficacy of the new MDT approach encouraged the World Health Organisation to develop a strategy to eliminate leprosy as a public health problem by 2000. This target was defined as a prevalence of less than 1 case per 10,000 population which was achieved in the year 2000. However, this decline in prevalence was not accompanied by a corresponding decline in incidence which remains at an annual estimate of about 200,000 new cases worldwide, with up to 10% of these cases being among children under the age of 15 years [10].

In 2016 the World Health Organisation Launched its 'Global Leprosy Strategy 2016 - 2020: Accelerating towards a Leprosy free world' to provide the final push towards leprosy control. Its goal was to reduce grade 2 leprosy disability rates to less than one case per 1 million population and the number of leprosy-related disabilities among paediatrics patients to zero, while maintaining the ultimate goal of having less than 1 case per 10,000 population [11].

The most recent data published by the WHO showed that a total of 208, 613 cases of leprosy was reported in 2018 from 127 countries, compared to 211, 009 cases in 2019; this represented a decrease of 1.2% [12]. A Global prevalence rate of 0.2 per 10,000 population for leprosy was also reported at the end of 2018 representing a decrease of 8501 cases. There were however increases in the America, eastern Mediterranean, European and Western regions of the WHO, which have been attributed to an increase in active case detection campaigns and contact screening, in addition to the normal leprosy control activity [11].

Leprosy is now termed a Neglected Tropical Disease endemic in parts of Africa, Asia and the Americas. There are also pockets of high prevalence even within these endemic countries, the reason for which is still unknown and a subject for research [13]. Data published by the WHO in 2018 showed that the highest burden of leprosy worldwide was concentrated in three countries spread across two continents; India had the highest burden with 120,338 cases, Brazil had 28,660 cases while Indonesia had 17,017 cases. Countries such as Nigeria, Democratic Republic of Congo, Ethiopia and Tanzania all had between 1,000 and 10,000 cases each, while Canada, Algeria and Mongolia reported no cases that year [14].

3. Microbiology of Leprosy

Hansen's disease is caused by *Mycobacterium leprae* and *Mycobacterium Lepromatosis*. The most common causative agent is *Mycobacterium leprae* which is an obligate intracellular, acid-fast bacillus with high infectivity and low pathogenicity [15]. The bacterium is non-motile, measures 4-7 μm long and can only be cultured on Mouse paw pads or the nine-banded Armadillo *(Dasypus novemcinctus)*. *M. Leprae* grows slowly, and aided by very low temperatures, it only divides once every twelve days [16,17]. In 2008, *Mycobacterium Lepromatosis* was identified in Mexico and has been shown to cause leprosy. *M. Leprae* and *M. Lepromatosis* have evolved from a common ancestor more than 13 million years ago and are similar in genome size. The protein coding genes have also been shown to share 93 percent nucleotide sequence identity [13].

Humans are the primary reservoir of *M. Leprae* but the nine-banded Armadillos *(Dasypus novemcinctus)*, Red Squirrel *(Sciurus vulgaris)* and the Mangabey monkeys have also been identified as natural reservoirs [15].

4. Transmission of Leprosy

Despite Leprosy being an age-old disease, there is still a poor understanding of its transmission routes. The skin and the upper respiratory tract are the most likely routes, with research favouring the upper respiratory tract. It is suggested that aerosol droplets from humans with leprosy can be inoculated onto the nasal mucosa of healthy individuals leading to a local infection and subsequent dissemination just like the case with tuberculosis [18].

Prolonged skin to skin contact can also lead to transmission especially when contact has been with a case of Lepromatous leprosy due to the high levels of *M. Leprae* in the superficial dermis of these patients. There have been cases from accidental needle injuries and tattooing [16,19]. There are also reports of transmission from direct or indirect contact with the nine-banded Armadillo [20].

The incubation period of *M. Leprae* varies especially in endemic areas; the average incubation period is between three years and ten years. This has been estimated from observational studies as there are no accurate immunological tests to identify the latent phase of the infection. There have been cases of Leprosy in infants just a few weeks old and in veterans decades after exposure [16]. In some endemic areas a considerable percentage of the population may be infected and remain asymptomatic, with a large proportion having spontaneous resolution in early phases of the disease. One major factor determining disease manifestation is the immune status of the exposed individual [17].

5. Pathogenesis of Leprosy

Mycobacterium Leprae mainly infects macrophages and Schwann cells leading to demyelination, loss of axonal conductance and nerve injury [21]. The bacteria infect the Schwann cells via a laminin binding receptor in addition to PGL1, a conjugate protein. Studies have also shown that *M. Leprae* targeted SC receptor, dystophin may also play a role in the binding of M. Leprae. Thereafter, there is a direct bacterial ligation to neuregulin receptor, ErbB2 and Erk1/2 activation, and subsequent MAP kinase signalling and proliferation leading to demyelination [22,23,24]. Cutaneous and mucosal involvement occur due to infection of histiocytes and keratinocytes [17].

6 Clinical Features and Classification

In 1966 Ridley and Jopling classified leprosy into the lepromatous leprosy and tuberculoid leprosy based on immune response. The lepromatous leprosy (LL) variants have a high burden of *M. leprae* due to a low cell mediated immunity with a humoral Th2 response, while the tuberculoid (TT) variants have a low mycobacterial burden due to a high cell mediated immunity with a Th1 response. In addition to these two extreme poles, there were three borderline forms of leprosy; borderline lepromatous, borderline borderline and borderline tuberculoid [25].

For therapeutic purposes, the World Health Organisation classified leprosy into Paucibacillary and Multibacillary leprosy based on the number of skin lesions or the skin smear results. In the classification based on skin smears, patients showing negative smears at all sites were grouped as Paucibacillary leprosy (PB), while those showing positive smears at any site are grouped as having Multibacillary leprosy (MB). However, most leprosy programs lack skin smear tests and use the number of skin lesions and nerve involvement to decide on the classification into Paucibacillary (less than five lesions) and Multibacillary leprosy (five or more skin lesions) [17].

The clinical variant of leprosy is dependent on the mycobacteria's tropism for the skin and peripheral nerves and by the hosts genetically determined susceptibility to *M. Leprae.* The disease only manifests in 5 - 10 percent of exposed individuals with a high prevalence of subclinical infection in endemic areas [17]. More so, there is a delay in diagnosis in non-endemic areas as patients may present to a wide range of specialists as this is not a common disease.

Indeterminate leprosy - This is the earliest manifestation of leprosy and a poor predictor of the subsequent course of the disease. It presents with poorly demarcated hypo-pigmented macules which can be smooth or scaly. These macules can also vary in number and site. Some patients may have sensory loss over macules and may even have thickened peripheral nerves Diagnosis is very difficult at this stage as dermatopathology or molecular biology techniques are of poor diagnostic value. This presentation can last up to 5 years and if this stage is not identified it progresses easily to more determinate forms depending on the host immune response [16,26].

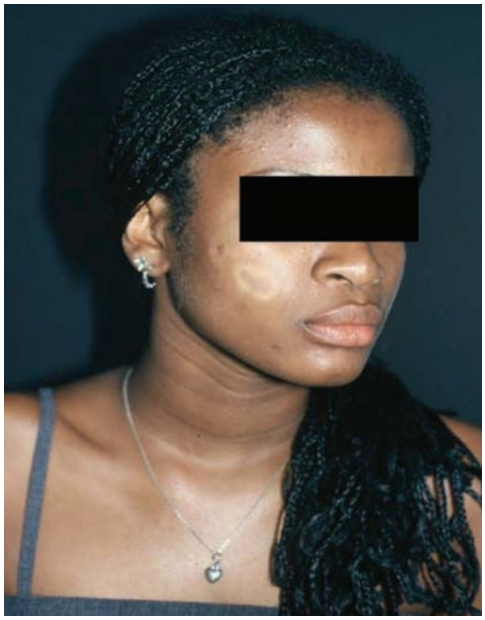

Figure 1. Indeterminate leprosy (source: Fischer 2017)

Tuberculoid leprosy - This presents in hosts with a good immune response. It is characterised by asymmetrically distributed plaques and papules on the extremities. These may coalesce into erythematous plaques with central atrophy and hypopigmentation. Some patients may have alopecia, anhidrosis, loss of pain and temperature sensation as well as loss of fine touch over skin lesions. Patients are hardly contagious as this is a predominately paucibacillary leprosy [27].

Lepromatous leprosy - This is characterised by multiple symmetric papules and nodules affecting the skin and mucous membranes. There is a strong predilection for the lower limbs and face, especially the earlobes. It leads to loss of eyebrows with a symmetrical Centro facial distribution of the cushion-like nodules referred to as leonine facies. Involvement of the nasal mucosae can lead to a destruction of the nasal septum and nasopharynx with associated ulcerations of the palate and larynx. Another serious complication associated with lepromatous leprosy is visual loss with complete blindness in 10 percent of patients. Other complications are glomerulonephritis, acute orchitis, amyloidosis and hepatitis and periportal fibrosis. [16,28]

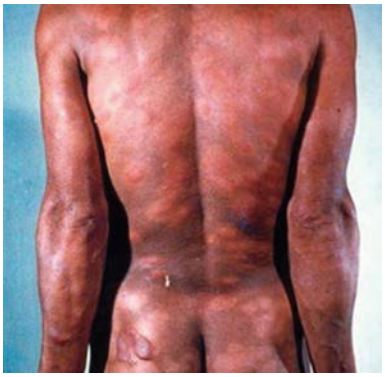

Figure 2. Lepromatous Leprosy (Source: Fischer 2017)

Intermediate leprosy/ Borderline Leprosy - In a significant number of cases leprosy presents as an intermediate form with variable degrees of tuberculoid and lepromatous manifestations. They have been classified into three groups based on the Ridley and Jopling classification

1 - Borderline Tuberculoid Leprosy - The skin lesions here are more numerous but less indurated when compared to tuberculoid leprosy. Its annular plaques and papules are sharply demarcated and asymmetrically arranged. Its asymmetric sensory and motor nerve involvement is less when compared to the tuberculoid form of leprosy. Patients with this variant may have a Tuberculoid leprosy upgrade or borderline leprosy downgrade depending on the change in immune response [17,25].

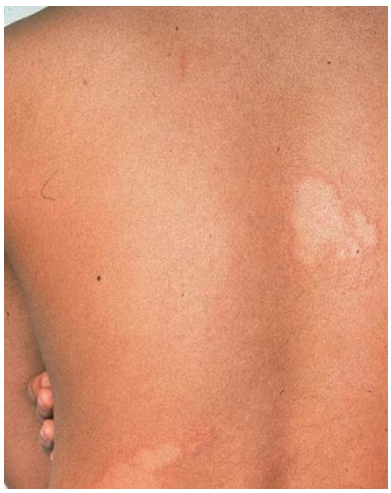

Figure 3. Borderline Tuberculoid Leprosy (Source: Fischer 2017)

2 - Borderline Lepromatous Leprosy - This is characterised by symmetrically distributed, multiple hypo-pigmented papules, nodules and plaques. These lesions are poorly demarcated with small islands of normal skin. There is also widespread peripheral nerve involvement with sweating and hair growth being rarely affected [17,29].

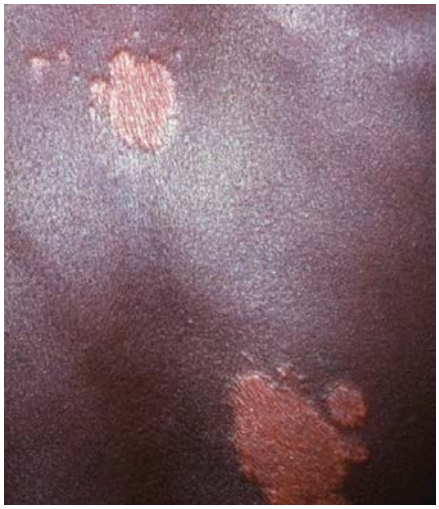

Figure 4. Borderline Lepromatous leprosy (Source: Fischer 2017)

3 - Borderline Borderline Leprosy - This form of leprosy is characterised by an overall increase in the number of skin lesions which are symmetrically distributed. These lesions can have features of both tuberculoid and lepromatous leprosy [17].

Histoid Leprosy - This is a distinct clinical and bacteriologic manifestation of Multibacillary leprosy. It is relatively uncommon and presents with numerous plaques and nodules on the back, buttocks, face and bony prominence. It could present as a primary manifestation of the disease or secondary to dapsone resistance [30].

Polyneuritic Leprosy - This is a recognised entity in the Indian subcontinent, presenting with only nerve involvement with no cutaneous manifestations. Nerves are thick, tender or both. Localised nerve abscesses have also been reported [31].

Neurological manifestations of leprosy

All forms of leprosy can affect the nerves and can even be the only presenting symptom. The extent of the nerve involvement depends to a great extent on the type of immune response to the mycobacteria [17].

Tuberculoid leprosy, despite the moderate nature of its cutaneous manifestations can progress to severe motor and sensory nerve damage despite adequate immune response. From a pathophysiologic point of view, this is due to the tropism exhibited by M. Leprae towards Schwann cells eventually leading to granuloma formation. This presents clinically with nerve thickening leading to pressure induced atrophy and loss of nerve function. It can also lead to cutaneous ulcerating abscesses at superficial nerve endings. The peripheral sensory and motor nerves of the face and limbs are also affected; this presents initially as paraesthesia and hyperaesthesia then subsequently as hypoesthesia and anaesthesia [17].

The progressive peripheral polyneuropathy can lead to trophic ulcers with superimposed infections which can result in osteomyelitis. Hyperkeratosis of the palms and soles of the feet are also common. Bone resorption in the phalanges can occur leading to bone loss with resultant auto-amputation. These types of peripheral polyneuropathy can progress rapidly or slowly without any neuropathic pain [17,31].

Lepromatous leprosy on the other hand is characterised by less perineural mycobacterial invasion and inflammation thus less mycobacteria are found in the Schwann cells of this variant. It is characterised by a distal peripheral neuropathy which is symmetrical. The borderline variants have been associated with one or more mono neuropathies leading to severe motor deficits as shown in the table below [17,30].

Nerves that are particularly affected by leprosy and palpable in advanced cases.

- Ulnar nerve in the ulnar groove.
- Median nerve prior to entering the carpal tunnel.
- Common peroneal nerve at the level of the fibular head.
- Posterior tibial nerve behind the medial malleolus.
- Superficial branch of the radial nerve; nerve compression syndrome (Wartenberg's syndrome) with sensory deficits (dorsoradial aspect of the hand).
- Sural nerve behind the lateral malleolus.
- Great auricular nerve at the posterior margin of the sternocleidomastoid muscle.
- Facial nerve, frontal branches and cervical branches.

7. Leprosy Reactions

Leprosy reactions refer to inflammatory episodes that complicate the otherwise largely languid course of leprosy [33,34]. They are acute hypersensitivity reactions which can occur prior to, during or after treatment for the disease. Two distinct types of leprosy reactions have been described affecting 30 to 50 percent of these patients; Type 1 leprosy reaction also known as reversal reaction and Type 2 reaction known also called erythema nodosum leprosum [33]. Type 1 reactions (T1R) occur in the borderline end of the spectrum (BL, BB and BT) while type 2 reactions occur with lepromatous leprosy (BL and LL). Despite extensive study, the underlying pathogenesis and triggers for reactions in leprosy remain poorly understood [35].

Type 1 reactions appears to result from spontaneous enhancement of cellular immunity and delayed-type hypersensitivity to M. leprae antigens, while type 2 reactions are considered to be an immune complex disorder even though this has yet to be proven [6]. Type 1 reactions are more gradual in onset (over a few weeks), are less associated with systemic symptoms although they can occur suddenly and if untreated, resolve over weeks to months. [33,35] Clinical features include erythema and induration of pre-existing lesions, skin ulceration, neuritis resulting in paralysis, deformity and new loss of sensation [36]. Type 2 reactions in contrast usually are sudden in onset and systemic manifestations are more common, with the natural course spanning 1 to 2 weeks although multiple recurrence is frequent [35,36]. Features include abrupt eruption of numerous tender nodules with no relationship to existing lesions. Others include neuritis with sensory and motor neuropathy, tender lymphadenopathy, orchitis, iridocyclitis, muscle tenderness, and arthritis/arthralgia [35,36].

Worth mentioning is Lucio's phenomenon which is a rare acute, severe, necrotizing vasculitis in patients with long standing lepromatous leprosy. It occurs primarily in patients of Mexican ancestry but has been reported in other countries as well. It presents with necrotizing, punched-out ulcerations that may be extensive in distribution and has a high morbidity and mortality [35].

8. Diagnosing Leprosy

The presence of classical signs is central to the diagnosis of leprosy with demonstration of the organism by slit skin smears, histopathology or PCR playing an ancillary role in supporting the diagnosis. Suspicion of leprosy should be entertained in the presence of symptoms including pale or reddish patches on the skin, loss or decreased sensation in the skin patches, numbness or tingling of the hands or feet, limb weakness, tender nerves, nodules on the face or earlobes, painless wounds or burns especially on hands and feet. [37]

Leprosy is diagnosed when at least one of the following cardinal signs is manifested:

• Definite loss of sensation in a hypopigmented or reddish skin patch.

• A thickened or enlarged peripheral nerve, with loss of sensation and/ or weakness of the muscles supplied by that nerve.

• The presence of acid-fast bacilli in a slit-skin smear. [37]

Diagnosis is definitively established when the physical signs above are combined with a skin biopsy confirming the presence of acid-fast bacilli. In endemic areas, clinical diagnosis is usually sufficient. In areas where leprosy is relatively uncommon however, skin biopsy can be helpful for diagnostic confirmation and/or to rule out other causes of disease [36]. Pauci-bacillary leprosy and early clinical stages pose a diagnostic challenge with the slit skin smears on account of absence of bacilli on smear testing. More advanced diagnostic methods including; Enzyme Linked immunosorbent Assay (ELISA), lateral flow assays and Polymerase chain reaction (PCR) based assays, while possibly helpful in PB leprosy pose their own challenges. ELISA and lateral flow assays have poor sensitivity for PB leprosy. PCR based assays while demonstrating higher accuracy, lack standardisation, are not widely available commercially and require significant technical expertise to run. In view of these challenges, the WHO recommends that based on currently available evidence, newer ELISA, lateral flow and PCR tests do not present a clear advantage over current standard diagnostic methods (clinical diagnosis with or without confirmatory tests such as slit-skin smear or biopsy) [41]. Unlike many other infectious diseases, there are no reliable serological or microbiological tests able to diagnose leprosy [38].

9 Treating Leprosy

The treatment of leprosy, with curative intent, involves the use of multi-drug therapy which includes a combination of rifampicin, dapsone and clofazimine. This combination of multiple drugs is intended to prevent the development of resistance which occurs with monotherapy as was demonstrated by resistance to dapsone when it was initially used as monotherapy [39].

The WHO first published guidelines for the treatment of leprosy using multi-drug therapy in 1982, as a response to the increasing reports of dapsone resistance. The treatment guidelines recommended using a combination of the above named three medications depending on whether treatment was for paucibacillary or multibacillary leprosy. For Paucibacillary leprosy, Rifampicin and dapsone were used for 6 months, while Multibacillary leprosy was treated for 2 years by adding clofazimine to rifampicin and dapsone. [39]. Further guidelines published in 1998, changed the duration of treatment of multibacillary leprosy to 12months while keeping the medications unchanged. [40]

The most recent WHO guidance published in 2018 now recommended a change to the treatment of paucibacillary leprosy. The guidelines now are that paucibacillary leprosy is treated with 3 medications (rifampicin, dapsone and clofazimine) for 6 months, in contrast to the previous 2 medications as detailed above. Thus, with the most recent changes, both forms of leprosy are treated with 3 medications with the only difference being the duration of therapy. [41]. The above WHO guidance differs from that used by the National Hansen disease programme in the United states which advocates for longer treatment. It recommends Rifampicin and dapsone for 12 months for

PB leprosy and rifampicin, dapsone and clofazimine for 24 months for MB leprosy. [38]

For rifampicin-resistant leprosy, the guidelines recommend treatment with at least two second-line drugs (clarithromycin, minocycline or a quinolone) plus clofazimine daily for 6 months, followed by clofazimine plus one of these drugs for an additional 18 months. When ofloxacin resistance is also present, a fluoroquinolone should not be used as part of second-line treatment. The regimen of choice in such cases should consist of 6 months of clarithromycin, minocycline and clofazimine followed by clarithromycin or minocycline plus clofazimine for an additional 18 months [41].

References

[1] Skinsnes O. Notes from the History of leprosy. International journal of leprosy. 1973; 41(2): 1.

[2] Browne S. Some Aspects of the History of Leprosy: The Leprosie of Yesterday [Internet]. Journals.sagepub.com. 1975 [cited 25 May 2020]. Available from: https://journals.sagepub.com/doi/pdf/10.1177/0035915775068008 0.

[3] Bennett BH, Parker DL. and Robson M. Leprosy: steps along the journey of eradication. Public Health Reports, 2008, 123(2), 198-205.

[4] Monot M, Honoré N, Garnier T, Araoz R, Coppée JY, Lacroix C, et al. On the origin of leprosy. Science; 2005, 308(5724): 1040-1042.

[5] Robbins G, Tripathy VM, Misra VN, Mohanty RK, Shinde VSG, Kelsey M. et al. "Ancient Skeletal Evidence for Leprosy in India (2000 B.C.)" PLOS ONE. 2000, 4(5): e5669.

[6] Trautman JR. A brief history of Hansen's disease. Bulletin of the New York Academy of Medicine. 1984;60(7):689-695.

[7] Venita J. The legacy of Armauer Hansen. A portrait in history. Archives of Pathology and Laboratory Medicine 2000; (4)124: 496-497.

[8] World Health Organisation. Leprosy fact sheet. 2000 Available from: https://www.who.int/news-room/fact-sheets/detail/leprosy (accessed 25/5/2020).

[9] Rao P N. Global leprosy strategy 2016-2020: Issues and concerns. Indian Journal of Dermatology, Venereology and Leprology [serial online (cited 2020 May 17) 2017; 83: 4-6.

[10] Victor SS, Carlos DFS, Paulo RS, Martin F and Luis E. Cuevas Leprosy: why does it persist among us? Expert Review of Anti-infective Therapy, 2020.

[11] World Health Organisation, Facts Sheet on Leprosy, 2019, (Cited 2020 June 02)Available at: https://www.who.int/en/news-room/fact-sheets/detail/leprosy.

[12] World Health Organisation, Neglected Tropical Diseases: News, 2019 ,(Cited 2020 June 02) Available at: https://www.who.int/neglected_diseases/news/Leprosy-new-data-show-steady-decline-in-new-cases/en/.

[13] Ploemacher T, Faber WR, Menke H, Rutten V, Pieters T. Reservoirs and transmission routes of leprosy; A systematic review. PLoS Neglected Tropical Diseases. 2020; 14(4): e0008276. Published 2020 Apr 27.

[14] World Health Organisation, Global Health Data Repository: Leprosy- Number of new leprosy cases Data per country (Cited 2020 May 24th).

[15] Oliveira IVP, Deps PD, Antunes JMAP. Armadillos and leprosy: from infection to biological model. Revista do Instituto de Medicina Tropical de Sao Paulo. 2019; 61: e44. Published 2019 Sep 12.

[16] Ramesh MB and Chaitra P. Leprosy: An Overview of Pathophysiology, Interdisciplinary Perspectives on Infectious Disease 2012: 181089. Published online 2012 sep 4.

[17] Marcellus F. Leprosy - an overview of clinical features, diagnosis, and treatment, Journal of the German society of dermatology August 2017 vol 15(08), 801-827.

[18] Job CK, Jayakumar J, Kearney M, Gillis TP. Transmission of leprosy: A study of skin and nasal secretions of household contacts of leprosy patients using PCR. The American Journal of Tropical Medicine and Hygiene. 2008; 78(3): 518-521.

[19] Satapathy J, Kar BR, Job CK. Presence of Mycobacterium leprae in epidermal cells of lepromatous skin and its significance. Indian Journal of Dermatology, Venereology and Leprology. 2005; 71(4): 267-269.

[20] Bruce S, Schroeder TL, Ellner K, Rubin H, Williams T, Wolf JE. Armadillo exposure and Hansen's disease: An epidemiologic survey in southern Texas. Journal of the American Academy of Dermatology. 2000; 43(2): 223-228S.

[21] Rambukkana, A, Zanazzi G, Tapinos, N., and Salzer, J L "Contact-dependent demyelination by Mycobacterium leprae in the absence of immune cells," Science, 2002, 296(5569), pp. 927-931.

[22] Marques MAM, Antônio VL, Sarno EN, Brennan PJ, and Pessolani MCV, "Binding of α2-laminins by pathogenic and non-pathogenic mycobacteria and adherence to Schwann cells," Journal of Medical Microbiology, 2001, 50(1), pp. 23-28.

[23] Tapinos N, Ohnishi M, and Rambukkana A, "ErbB2 receptor tyrosine kinase signaling mediates early demyelination induced by leprosy bacilli," Nature Medicine, 2006, 12(8), pp. 961-966.

[24] Rambukkana A, Yamada H, Zanazzi G, Mathus T, Salzer JL Yurchenco PD et al., "Role of α-dystroglycan as a Schwann cell receptor for Mycobacterium leprae," Science, 1998, 282(5396), pp. 2076-2079.

[25] Ridley DS. and Jopling WH. "Classification of leprosy according to immunity. A five-group system," International Journal of Leprosy and Other Mycobacterial Diseases,1966, 34(3), pp. 255-273.

[26] Fajardo TT, "Indeterminate leprosy: a five year study, clinical observations," International Journal of Leprosy, 1973, Vol 41, p. 576.

[27] Canizares O, Harman R, Adriaans B. Leprosy. In: Canizares O, Harman R, editors. Clinical Tropical Dermatology. 2nd ed. Boston: Blackwell Scientific; 1992. pp. 165-200.

[28] Elinav H, Palladas L, Applbaum YH, Gilead L, Moses AE, Cohen-Poradosu R. Plantar ulcers and eyebrow-hair paucity. Clinical Infectious Diseases. 2006; 42(5): 684-685, 722-724.

[29] Akpolat ND, Akkus A and Kaynak E. An Update on the Epidemiology, Diagnosis and Treatment of Leprosy, (Cited 2020 July 3rd): 2018.

[30] Sehgal VN and Srivastava G, "Status of histoid leprosy-a clinical, bacteriological, histopathological and immunological appraisal," Journal of Dermatology, 1987, 14(1), pp. 38-42, 1987.

[31] Sehgal VN, Tuli MS, and Dube B, "Leprotic nerve abscesses in northern India," International Journal of Leprosy and Other Mycobacterial Diseases, 1967, 35(1), pp. 60-64.

[32] Britton W. Leprosy. In: Cohen J, Powderly WG, editors. Infectious Diseases. London: Mosby; 2003. pp. 1507-1513.

[33] Walker SL. 2020 Leprosy reactions. In Gillis TP (ed), International textbook of leprosy. Accessed 13/6/2020.

[34] Scollard DM et al. 1993. Epidemiological characteristics of leprosy. International journal of leprosy. Volume 62, No 4. Available from http://ila.ilsl.br/pdfs/v62n4a09.pdf. Accessed 13/6/2020.

[35] Scollard DM et al. The continuing challenges of leprosy. Clinical microbiology reviews. 2006; 19(2): 338-381.

[36] Scollard D et al. 2020 Leprosy; epidemiology, microbiology, clinical manifestations and diagnosis. In Baron, E (ed). Uptodate. Accessed 13/6/2020 https://www.uptodate.com/contents/leprosy-epidemiology-microbiology-clinical-manifestations-and-diagnosis?search=diagnosis%20of%20leprosy&source=search_result&selectedTitle=1~95&usage_type=default&display_rank=1#H15.

[37] World health organisation. Guidelines for the diagnosis, treatment and prevention of leprosy. Available from https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?sequence=10&isAllowed=y. Accessed 13/6/2020.

[38] National Hansen disease programme. NHDP guide to the management of Hansen disease. Available from https://www.hrsa.gov/sites/default/files/hrsa/hansens-disease/pdfs/hd-guide-management.pdf. Accessed 13/6/2020.

[39] WHO Study Group on Chemotherapy of Leprosy for Control Programmes & World Health Organization. (1982). Chemotherapy of leprosy for control programmes: report of a WHO study group World Health Organization. https://apps.who.int/iris/handle/10665/38984. Accessed 12/6/2020.

[40] WHO Expert Committee on Leprosy. WHO Expert Committee on Leprosy: seventh report. WHO Technical Report Series No. 874. Geneva: WHO; 1998. http://www.who.int/iris/handle/10665/42060, Accessed 20th June 2020.

[41] Guidelines for the diagnosis, treatment and prevention of leprosy. New Delhi: World Health Organization, Regional Office for South-East Asia; https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?ua=1 Accessed 20th June 2020.