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A REVIEW ON: LEPROSY IN THE 21ST CENTURY: TREATMENT, FUTURE DIRECTIONS AND SYSTEMATIC

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ABSTRACT

Leprosy, or Hansen's disease, is a chronic granulomatous infection primarily caused by Mycobacterium leprae and Mycobacterium lepromatosis, which is mainly transmitted through person-to-person contact and has a long incubation period of 2–6 years. It primarily affects the skin and peripheral nerves and is still endemic in various regions of the world. Leprosy is associated with disability and marginalization. Diagnosis is clinical and is made when the patient has at least 1 of the following cardinal signs specified by the World Health Organization: hypopigmented or erythematous macules with sensory loss; thickened peripheral nerves; or positive acid-fast skin smear or skin biopsy with loss of adnexa at affected sites. Leprosy is treated with a multidrug combination of rifampicin, clofazimine, and dapsone. Two main regimens are used depending on whether the patient has paucibacillary or multibacillary disease. Hansen's disease treatment and outlook for patients since the introduction of multidrug therapy (MDT) 3 decades ago, the global incidence remains high, and patients often have long-term complications associated with the disease. In this article, they recent findings related to genetics, susceptibility, and disease reservoirs and the implications of these findings for Hansen's disease control and health outcomes for patients. They are continued difficulties associated with treatment of inflammatory episodes known as "leprosy reactions," which cause much of the disability associated with the disease and can affect people for many years after MDT is complete. "As the world strives for zero leprosy transmissions, this review bridges the gap between historical insights and cutting-edge research. Discussing innovations in diagnostics, therapeutics, and prevention, it emphasizes the imperative of integrated approaches, community engagement, and intensified

research to vanquish this ancient affliction and secure a leprosy-free future." The purpose of this review is to provide an up-to-date analysis of leprosy, focusing on recent discoveries in genetics, susceptibility factors, and carriers of the disease. These results have implications for patient outcomes and management of leprosy. This review aims to fill this gap by providing updated diagnostic and treatment recommendations for adults and children with leprosy.

KEYWORDS: Hansen's disease, Mycobacterium lepromatosis, pathophysiology, risk factors, epidemiology, global health, treatment, future directions.

1. INTRODUCTION

Leprosy is a chronic infection caused by the bacterium Mycobacterium leprae, which can affect various parts of the body, including the skin, peripheral, upper respiratory tract, and in men, the testes. It is transmitted primarily through prolonged contact, often via nasal secretions or aerosols carrying bacterial droplets. Interestingly, despite its contagious nature, most people (about 95%) have natural immunity and can resist the infection. There is also a risk of vertical transmission, where the disease can be passed from an infected mother to her baby through the placenta.[1]

The disease is caused by an obligate intracellular bacillus, Mycobacterium leprae, which was identified in the19th century by the Norwegian physician Gerhard HenrikArmauer Hansen.[3]

Leprosy are despite curative treatment being available, leprosy is still prevalent worldwide, with little change in annual cases observed in the past decade. The WHO South East Asia region is the worst affected, accounting for over 70% of new cases. One reason leprosy transmission still occurs is non-adherence to multi-drug therapy.

In the 21st century, despite advances in scientific research, leprosy remains a very prevalent disease. In Brazil, the goal of eliminating the disease is part of the Public Health policy that proposes the offer of curative treatment, with increased access to health services, through the decentralization of control actions for basic health services.[4]

2. EPIDEMIOLOGY OF LEPROSY

The introduction of multidrug therapy (MDT) worldwide by the World Health Organization (WHO) in 1982 in response to the increasing number of cases of dapsone resistant leprosy was instrumental in reducing the number of new cases of leprosy worldwide from 5.4 million in the early 1980s to 210,000 cases in 2014.[5]

In 2016, the World Health Organization (WHO) introduced the Global Leprosy Strategy 2016-2020, an ambitious plan to accelerate progress toward a world without leprosy. According to WHO data from 2018, the global burden of leprosy is concentrated primarily in two continents and three countries. India reported the most cases, with 120,338, followed by Brazil with 28,660, and Indonesia with 17,017.

According to the latest WHO data, 208,613 cases of leprosy were reported in 127 countries in 2018. In 2019, the number of cases decreased slightly by 1.2% to 211,009 cases.[6]

A total of 244 796 new cases were registered in 2009, with southeast Asia having the largest number (166 115 cases); at the beginning of 2010 the worldwide prevalence was 211 903 cases; and recently 107851 cases were registered in 2023, with India.[10]

3. CLASSIFICATIONS OF LEPROSY ACCORDING TO WHO

The World Health Organization (WHO) developed a simpler classification system for settings with limited clinical or laboratory resources.

A. Paucibacillary (PB) Leprosy: Five or fewer skin lesions without detectable bacilli on skin smears. A single lesion is classified as single-lesion PB.

Symptoms

One or more hypopigmented (lighter colour) or erythematous (red) skin patches or lesions.
Loss of sensation or numbness in affected skin areas.
Enlarged peripheral nerves.
Weakness or muscle atropy (rare).

Treatment

1. WHO-recommended regimen: 6-month treatment with:
Rifampicin (600 mg/month) b. Dapsone (100 mg/day)
2. Alternative regimens: May include chloramine or other antibiotics.

Prognosis

1. Generally good, with early treatment
2. Low risk of disability or disfigurement
3. High cure rate (>95%)

Complications (rare)

1. Nerve damage or neuropathy
2. Relational states (e.g., Type 1 or 2 reactions)
3. Disability or disfigurement (if left untreated)

Prevention

1. Early detection and treatment
2. Vaccination offers some protection
3. Avoid close contact with untreated leprosy patients

B. Multibacillary (MB) Leprosy: Six or more lesions, with bacilli present on skin smears.

Symptoms

1. Multiple hypopigmented or erythematous skin patches or lesions
2. Numbness, tingling, or loss of sensation in hands/feet
3. Weakness or muscle atrophy
4. Enlarged peripheral nerves (e.g., ulnar, peroneal)
5. Disfigurement (e.g., nodules, plaques)
6. Eye involvement (e.g., dryness, ulcers)

WHO Treatment Guidelines

1. Rifampicin (600 mg) once a month for 12 months
2. Dapsone (100 mg) daily for 12 months
3. Clofazimine (300 mg) monthly for 12 months + 50 mg daily

Treatment Duration : 12 months

WHO Recommendations

1. Integrated leprosy services into general healthcare
2. Early case detection and treatment
3. Post-treatment follow-up
4. Prevention of Disability and Disfigurement (PDD)

Complications

1. Permanent nerve damage
2. Disfigurement
3. Vision loss

4. Disability

Prevention

1. Early detection and treatment
2. Vaccination (Bacillus Calmette-Guérin, BCG) offers some protection
3. Avoid close contact with untreated leprosy patients.

4. TYPES OF SKIN LESIONS IN LEPROSY

4.1. Tuberculoid Leprosy (TT): Characterized by large, hypopigmented or erythematous lesions with well-defined borders and raised edges. These lesions often appear scaly.[12]

4.2. Borderline Leprosy (BL): BB is the immunologic midpoint or mid-zone of the granulomatous spectrum, being its most unstable area, with patients quickly up or downgrading to a more stable granulomatous posture with or without a clinical reaction. Characteristic skin changes are annular lesions with sharply marginated interior and exterior margins, large plaques with islands of clinically normal skin within the plaque, giving a "Swiss cheese" appearance.[13]

4.3. Borderline Tuberculoid (BT): Presents with target-like macules, usually on one side of the body. The number of lesions is greater than in TT. These lesions fall under the paucibacillary category in the WHO classification.[13]

4.4. Mid-Borderline (BB): Features “punched out” lesions resembling either BT or borderline lepromatous leprosy. The central areas of these lesions are usually anesthetic.[14]

4.5. Borderline Lepromatous Leprosy (BLL): This type includes erythematous macules, nodules, or papules that do not follow a specific pattern. The lesions are irregularly distributed and poorly demarcated, with some normal patches of skin between them.

4.6. Lepromatous Leprosy (LL): Inadvanced cases, this form may cause hair loss, nodular enlargement of the earlobes, and mucosal involvement that can mimic symptoms of a common cold. Without treatment, it can lead to complications such as aperforatedseptum.[15]

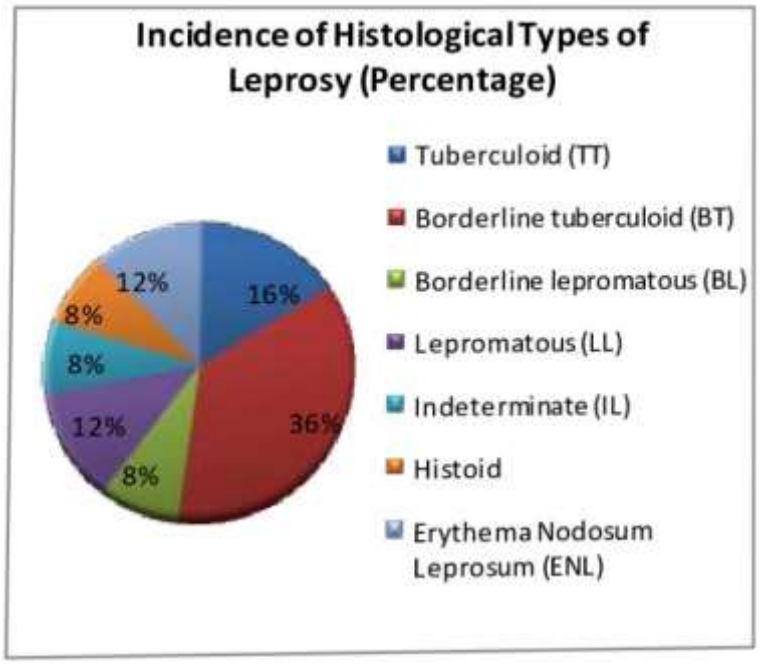

Fig. No. 01: Percentage incidence of Various histological Type of Leprosy.

FIG. No. 02.:- A 23-year-old female with the tuberculoid leprosy form, manifesting as a single well-defined hypopigmented macular lesion associated with anesthesia.

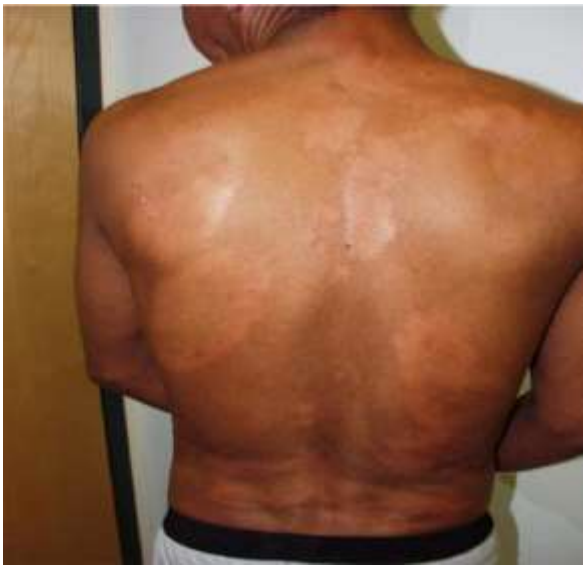

FIG. No. 03.:- A 42-year-old male with borderline tuberculoid leprosy, manifesting as multiple (5) polymorphic, partially raised, confluent, hypopigmented macules associated with anesthesia. The patient also had irregular enlargement of several large nerves in an asymmetrical pattern.

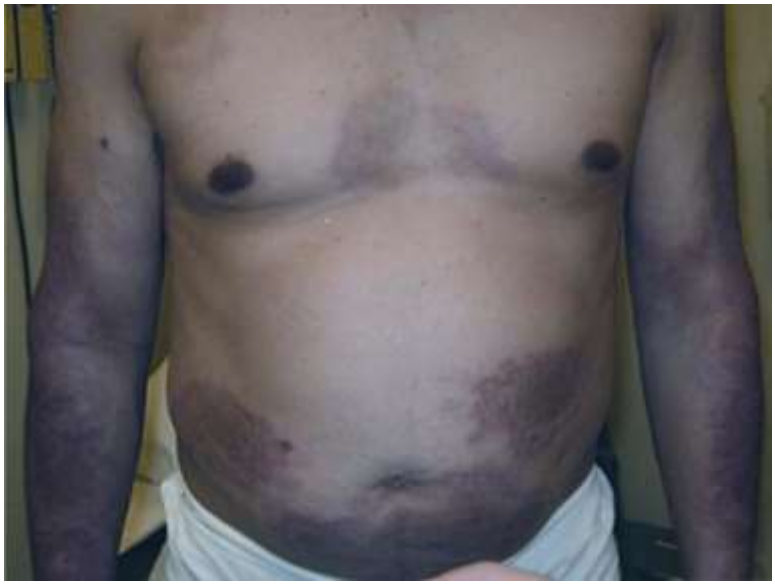

FIG. No. 04.:- A 53-year-old male with the borderline border line form of leprosy, manifesting as multiple infiltrated plaques with punched-out centers associated with anesthesia. The patient had many nerves involved in a symmetrical pattern.

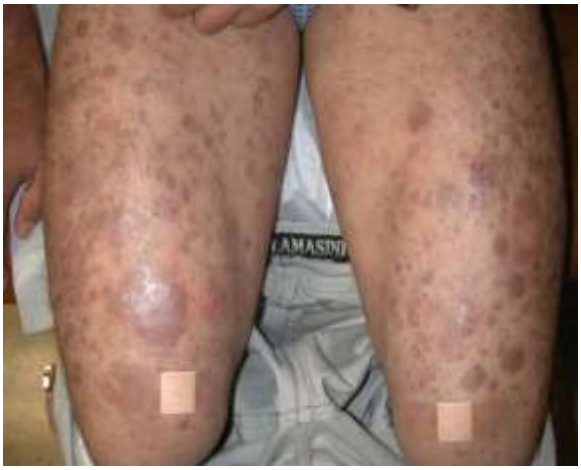

FIG. No. 05. :- A 29-year-old male with the borderline lepromatous form of leprosy, presenting with diffuse thickening of the skin with associated anesthesia and paresis.

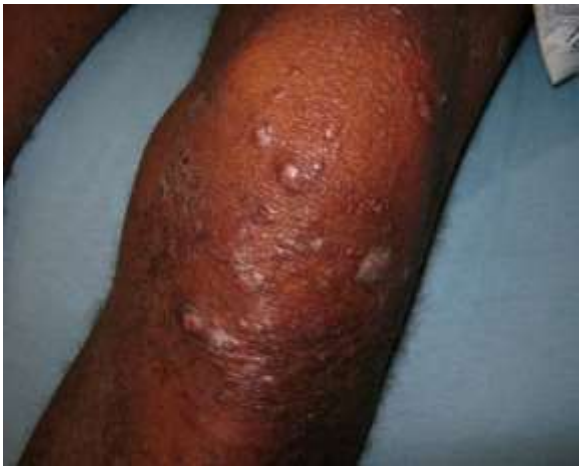

FIG. No. 06. :- A 17-year-old male with the lepromatous leprosy form of leprosy, manifesting as diffuse thickening with innumerable discrete as well as confluent nodules.

THE HD BACILLUS AND ITS IMPACT

HD results from infection with Mycobacterium leprae, an intracellular acid-fast bacillus. Most people (an estimated 95% of the world's population) are not genetically susceptible to the disease.[16]

There seems to be littlepathogen variability and virulence to explain the different clinical forms, with the possible exception of the recently discovered species Mycobacterium lepromatosis in patients with HD who had diffuse leprosy of Lucio and Latapí.[17,18,19]

Confirmation of this as a new species that could cause HD requires further research, as defined by Gillis et al.[20]

For example, among populations of the Western Pacific, particularly Micronesia, the prevalence (number of cases per 10,000 people) is among the highest in the world.[21]

Reactions have been categorized into two primary types: type 1 reactions, also known as reversal reactions (RRs), and type 2 reactions, or erythema nodosumleprosum (ENL) reactions.

TYPE 1 REACTION (T1R) [REVERSAL REACTION]

Type 1 responses are characterized by a spontaneous increase in cellular immunity and the development of delayed hypersensitivity to leprosy antigens.

This response involves the activation of immune cells to combat the presence of these microbial antigens in the body.[23,24] Type 1 reactions usually develop slowly over several weeks. If left untreated, these reactions usually gradually disappear over several weeks or months.[25,26]

T1R typically occurs in patients with borderline tuberculoid (BT), mid-borderline (BB), or borderline lepromatous (BL) leprosy.[27] It is characterized by:

Red, swollen areas in existing lesions, particularly around nerve trunks or the face

Erythema of skin lesions

Inflammation that can lead to deformity and paralysis

Edema

Ulceration of skin lesions

Weakness or loss of nerve function

5.2. TYPE 2 REACTION (T2R, ENL) [ERYTHEMA NODOSUM LEPROSY]

Type 2 reactions usually occur abruptly and areoften accompanied by a wide range of systemic symptoms.[28,29]

A type II reaction to erythema nodosum (ENL) is a type III humoral hypersensitivity reaction.[30]

T2R, or erythema nodosumleprosum (ENL), occurs in patients with borderline lepromatous (BL) and lepromatous leprosy (LL).[33]

Risk factors for T2R include puberty, pregnancy, and lactation.[35] Increased levels of TNF-alpha and other cytokines have been observed, but their exact role in the process remains unclear.[36]

Deposition of immune complexes in tissue, blood and lymphatic.
May experience sensory and motor neuropathy.
Multiple small red painful nodules and nodules form pustules.
Polymorphic lesions.
Painful lymphadenopathy, orchitis, iridocyclitis.
Neuritis with myalgia and arthitis/arthralgia.

PATHOPHYSIOLOGY

It is thought to be passed from person to person through nasal droplets and secretions. Casual contact and short-term contact does not seem to spread the disease transmission is by aerosol spread from infected nasal secretions to exposed nasal and oral mucosa The incubation period for leprosy is 6 months to 40 years or longer.

It affects the superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, anterior chamber of the eyes, and the testes.

Tissue damage depends on the degree to which cell- mediated immunity is expressed, the type and extent of bacillary spread and multiplication, the appearance of tissue-damaging immunologic complications (i.e. leprareactions) then result of nerve damage.

RISK FACTORS

Several factors increase the risk of contracting leprosy

Close Contact: Direct contact with an individual with leprosy significantly increases the likelihood of contracting the disease compared to the general population.

Armadillo Exposure: In the southern United States, although the exact transmission route

from armadillos to humans is not fully understood, molecular typing has confirmed that such zoonotic transfer does occur.[37]

Age: Older individuals are at higher risk of developing leprosy, with some studies showing a bimodal distribution of risk, with peaks between the ages of 5 to 15 and after 30.

Genetic Influences: Genetics plays a crucial role in the immune response to M. leprae. Specific genetic factors, such as the PARK2/PACRG gene, have been associated with innate immunity.[38]

Immunosuppression: Immunosuppressed individuals, such as those who have undergone organ transplantation, chemotherapy, or treatment for HIV, or those receiving immunosuppressive agents for rheumatologic conditions, are at an increased risk of developing leprosy.[39]

8. CLINICAL

Leprosy, caused by the bacterium Mycobacterium leprae, presents in a variety of forms due to the wide range of immune responses it triggers.[40] The Ridley-Jopling classification system categorizes the disease based on clinical features, ranging from a strong immune response with a small number of organisms (TL) to a weak immune response with a high number of organisms (LL).[41]

9. CLINICAL FEATURES

Table No. 01: Characteristics of ridley-Jopling Classification.

Characteristics	Tuberculoid	Borderline tuberculoid	Midborderline	Borderline lepromatous	Lepromatous leprosy
Number of lesions	Single or upto 3	A Few (up to 10)	Several (10–30)	Numerous, asymmetrical (>30)	Innumerable, symmetrical
Size	Variable, usually large	Variable, some are large	Variable	Small, some can be large	Small
Surface changes	Hypopigmented	Dry, scaly, look bright, and infiltrated	Dull or slightly shiny	Shiny	Shiny
Sensations	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Minimally diminished
Hair growth	Nil	Markedly diminished	Moderately diminished	Slightly diminished	Not affected initially

Skin smear	Negative	Negative or 1+	1–3+	3–5+	Plenty, including globi (6+)
Lepromin test	Strongly positive	Weakly positive	Negative	Negative	

10. TREATMENT OF IMMUNOLOGIC REACTION

Immune reactions, which are inflammatory responses, can occur before, during, or after treatment completion. These reactions can lead to nerve damage, paralysis, and deformity if not properly managed.

10.1. Type 1 Reaction (T1R): Mild cases may require supportive care, while severe cases with neuritis often necessitate corticosteroid treatment to prevent irreversible nerve damage.[44,45] Prednisone (40-60 mg/day) is commonly used, with gradual tapering as symptoms improve. Methotrexate may be used as an alternative in patients wiith diabetes.[46]

10.2. Type 2 Reaction (T2R, ENL): Severe cases require immediate corticosteroid therapy to prevent nerve damage. Prednisone (40-60 mg/day) is typically used, with dosage tapering over at least two weeks once the condition is under control.[47] Clofazimine may be used in chronic cases, though it is less effective for acute reactions. Thalidomide is also highly effective in treating ENL but poses significant risks for women of childbearing age.[48]

11. SOCIAL, ECONOMIC, AND ENVIRONMENTAL FACTORS IN HDTRANSMISSION AND CONTROL

11.1. Structural Inequality

While the proximate cause of HD is infection with M. leprae bacilliamong individuals with genetic susceptibility, there are many social determinants, as termed by the World Health Organization[49], that are associated with the continuation of this disease increase of endemicity.

These determinants include social and cultural factors but also the conditions of everyday life and structural inequalities that affect overall health and immunity.[50]

Future research that further examines the specific ways in which living conditions might be related to HD susceptibility could identify changes or improvements that will impact not only HD control efforts but also other areas of health (i.e. other neglected tropical infections) and quality of life in areas of endemicity.

11.2. International Migration

Some of the latest challenges facing HD control are not necessarily new. The movement of peoples within nations and around the globe has always been a factor in shaping the epidemiological portrait of HD. However, migration poses unique challenges to HD control in the 21st century.

In the United States, for example, although there is a National Hansen's Disease Clinical Center and a network of regional Hansen's disease clinics around the country, many U.S. physicians are not familiar with these options.

International migration is an issue not only in terms of patients receiving a diagnosis but also in terms of the long-term, sometimes lifelong care that many people require.

Stigma in the context of international migration is also an important concern.

Stigma may also arise during the medical encounter in cases where health care workers carry their own stigmatizing ideas about the disease.

11.3. HD COMMUNITIES AND COLONIES IN THE 21st CENTURY

Providing services for people affected by HD (and their families) who are living in communities that resulted from societal stigma or forced isolation is another important challenge that has received little global attention, since it is not viewed to be a significant concern in terms of controlling the disease.

Future research may identify unmet health, social, and economic needs for these HD communities around the world, but researchers should also attempt to note the specific challenges faced by residents of these communities in different national and cultural contexts.[61]

12. EVALUATION OF LEPROSY

The evaluation of leprosy relies heavily on laboratory techniques, particularly histopathological analysis through skin biopsies and polymerase chain reaction (PCR).[63] These methods, along with serologic tests, provide critical insights into the diagnosis and understanding of leprosy.

Drug Resistance

Historically, drug resistance in M. leprous was not a significant concern, but recent studies indicate a rising trend.[64,65] A study from 2009 to 2015 involving over 1,900 patients showed the following resistance rates:

- Rifampin: 3.8%
- Dapsone: 5.3%
- Ofloxacin: 1.3%

13. TREATMENT

13.1. The Indian government has recommended Dapsone, a crucial medication for treating leprosy, as follows

A. Paucibacillary patients

Dapsone - 100 mg daily – 6 months

Rifampicin - 600 mg once a month

After completing the 6-month course of dapsone treatment, continued treatment is determined based on the patient's condition. It is important to closely monitor patients for at least 2 years after treatment to ensure long-term effects and monitor potential relapses or side effects.[69]

B. Multibacillary patients

Dapsone 100mg daily - for initial 2 weeks

Rifampicin 600 mg daily- for initial 2 weeks. After that the treatment is given for 2 years.

Dapsone 100mg daily. Rifampicin 600mg once a month

Clofazamines 50mg daily.

To ensure ongoing monitoring and maintenance of health and treatment effectiveness, it is recommended that daily treatment diagnostic examinations and regular follow-up examinations continue for 5 years.

Duration of treatment

Paucibacillary leprosy for 6 months.

Multibacillary leprosy for 12 months.

Educate the people regarding multidrug therapy.

Educate how to take medicine, storage of medicines, side effects of medicines, etc.

Explain about the duration of treatment.

14. FUTURE DIRECTIONS

HD continues to represent a significant global health problem and one for which we are still lacking answers for many aspects of the natural history of the disease. Gelber and Grosseto suggest that as resources for HD control are diminishing, HD may “reemerge” as a significant problem.[70] In a recent commentary article, Scollard noted that the shift from confinement to out patient treatment of HD, although unquestionably better for patients’ families and social lives, has resulted in fewer opportunities for research on the disease.[71]

Although greater access to MDT may be achieved through horizontalization, health posts that act primarily as pharmaceutical distribution locations cannot provide the same quality of care as centers with physicians, physical therapists, psychologists, and social workers familiar with HD and its long-term physical and social effects.[72]

The findings of a number of studies contributed to the development of this test, which is being produced by the Infectious IDRI in conjunction with Orange Life Laboratories in Rio de Janeiro, Brazil.[73,74]

Funding for HD research and interest among scientists in nations where the disease is and is not endemic might be generated through the suggestion that understanding more about M. leprae, its effects on the body, and its evolution as a bacillus can give us insight into many other diseases and conditions as well as a greater understanding of population genetics.[75,76] For example, a study demonstrating the ability of M. leprae bacilli to reprogram Schwann cells in the human body to become more like stem cells may have applications for stem cell research in the future.[77]

15. CONCLUSION

Leprosy, or Hansen's disease, remains a significant public health concern despite its relatively low transmissibility and the availability of effective treatments. Caused by Mycobacterium leprae and Mycobacterium lepromatosis, leprosy primarily affects the skin and peripheral nerves, leading to characteristic symptoms such as numbness and skin lesions. Key risk factors for leprosy include close contact with infected individuals, exposure to armadillos in certain regions, age, genetic predisposition, and immunosuppressant. Understanding these factors can help in identifying at-risk populations and implementing targeted preventive measures.

In conclusion, although our understanding of leprosy has advanced significantly in the 21st century, there are still challenges to comprehensively addressing this ancient disease. Children not only suffer from leprosy but also play a critical role in the epidemiology of disease transmission. The integration of clinical, bacteriological, and immunological diagnostic techniques has improved our ability to more effectively detect and treat leprosy, but there are still challenges in applying these advances globally. This includes developing more sensitive and specific diagnostic tools, optimizing treatment regimens to prevent drug resistance, and establishing comprehensive strategies to combat the stigma associated with leprosy.

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