International Journal of Medical Studies
Available online at www.ijmsonline.in

INTERNATIONAL JOURNAL OF MEDICAL STUDIES
ESTD 2015

IJMS 6(1), 1-14 (2021)
Print ISSN 2542-2766

Chemoprophylaxis in individuals having close contact with morbus hansen patients: a review article

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Article history
Received 02 Jan 2021
Received in revised form 22 Jan 2021
Accepted 23 Jan 2021
Available online 31 Jan 2021

ABSTRACT

Introduction: Early detection of Morbus Hansen disease in individuals who have contact with Morbus Hansen patients and chemoprophylaxis is the main strategy in breaking the chain of spread of Morbus Hansen's disease. Various studies have shown that administration of chemoprophylaxis or in combination with immunoprophylaxis in individuals who have contact with the Morbus Hansen patient is quite effective in reducing the detection rate of new Morbus Hansen cases in endemic areas. There are various drug

options that can be used as chemoprophylaxis in individuals who have contact with the patient Morbus Hansen. Unfortunately, the effectiveness of the existing prophylactic regimen is not satisfactory, especially because it was found that various strains of M. leprae were resistant to various types of drugs.

Discussion: Several antibiotics have been shown to have both bacteriostatic and bactericidal activity against Mycobacterium leprae. An effective chemoprophylactic strategy not only takes into account the choice of drug type, dosage, and frequency of administration, but also the ideal number and type of contact individuals for Morbus Hansen patients who need to be traced, examined and given treatment. Based on observations, the acceptance of individual contacts to the program. The effectiveness of giving chemoprophylaxis to contact individuals as well as chemoprophylaxis in mass populations in endemic areas has been evaluated in various studies.

Conclusion: The Morbus Hansen control program has been quite successful in reducing the incidence of Morbus Hansen disease worldwide since the implementation of the MDT treatment program in Morbus Hansen patients. However, the detection rate of new Morbus Hansen cases, especially in endemic areas, remains high. Therefore, the Morbus Hansen disease eradication program also includes early detection of Morbus Hansen cases in individuals who come into contact with Morbus Hansen patients as well as prophylaxis to prevent the onset of Morbus Hansen disease.

Keywords: Contact, Morbus Hanses, Chemoprophylaxis

This article reviewed by Dr. Prateek, Dr. Ram. Edited by Dr. Pradeep J., Dr. S Gaur. Available online 31 Jan 2021.

INTRODUCTION

Leprosy or Morbus Hansen (MH) is a chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis. This disease is named after its discoverer, Hansen and is a granulomatous inflammatory disease of the peripheral nerves and mucosa of the upper respiratory tract. Skin lesions are early visible sign. If left untreated, Morbus Hansen's disease can become progressive and cause permanent damage to the skin, nerves, arms,

legs, and eyes. Morbus Hansen disease has been known for a long time, which is more than 4000 years, namely during the civilization of China, Egypt and ancient India. Morbus Hansen can be found all over the world, but this disease is endemic in certain areas, such as Africa, Southeast Asia and South America. In 1995, WHO estimated that at least 2 to 3 million people worldwide became permanently disabled because of Morbus Hansen [1].

Early detection of disease and appropriate treatment using a Multidrug Therapy (MDT) regimen are the foundation stones of the Morbus Hansen disease eradication program. Since the introduction of MDT use in 1981, more than 15 million MH patients worldwide have received treatment. The use of MDT has also reduced the prevalence rate of Morbus Hansen's disease from 5.2 million patients in the 1980s to about 200 000 patients this decade. The transmission of Morbus Hansen is suspected through several mechanisms, including: air droplets, children to parents, parents to children, siblings, length of exposure to Morbus Hansen patients, genetics and environmental conditions [1]. Risk factors for the occurrence of Morbus Hansen disease, among others: living in an endemic area of Morbus Hansen, low socio-economic conditions, such as poor living facilities, contaminated water, poor nutrition and other diseases that can reduce the body's immune system [1, 3]. Contact with a patient with Morbus Hansen is undoubtedly risk factors for contracting Morbus Hansen's disease [1-7].

Early detection of Morbus Hansen disease in individuals who have contact with Morbus Hansen patients and chemoprophylaxis is the main strategy in breaking the chain of spread of Morbus Hansen's disease [4]. Various studies have shown that administration of chemoprophylaxis or in combination with immunoprophylaxis in individuals who have contact with the Morbus Hansen patient is quite effective in reducing the detection rate of new Morbus Hansen cases in endemic areas [8].

There are various drug options that can be used as chemoprophylaxis in individuals who have contact with the patient Morbus Hansen. Unfortunately, the effectiveness of the existing prophylactic regimen is not satisfactory, especially because it was found that various strains of M. leprae were resistant to various types of drugs [7]. Aim of this study to review the effectiveness of chemoprophylaxis drug in individuals who have close contact with Morbus Hansen patients.

Morbus Hansen (MH) is named after the founder of this disease in the 19th century; a doctor from Norway named Gerhard Henrik Armauer Hansen. Morbus Hansen is a chronic infectious disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis. Mycobacterium lepromatosis was found as a Morbus Hansen pathogen in an endemic case that occurred in Mexico and the Caribbean in 2008 [1, 10, 11]. In Ziehl-Nielsen Staining, Mycobacterium leprae will be red [1]. Mycobacterium sp. has a characteristic rod-shaped, gram-positive, covered by a cell membrane consisting of a waxy layer, is acid resistant, aerobic, and intracellular obligate.

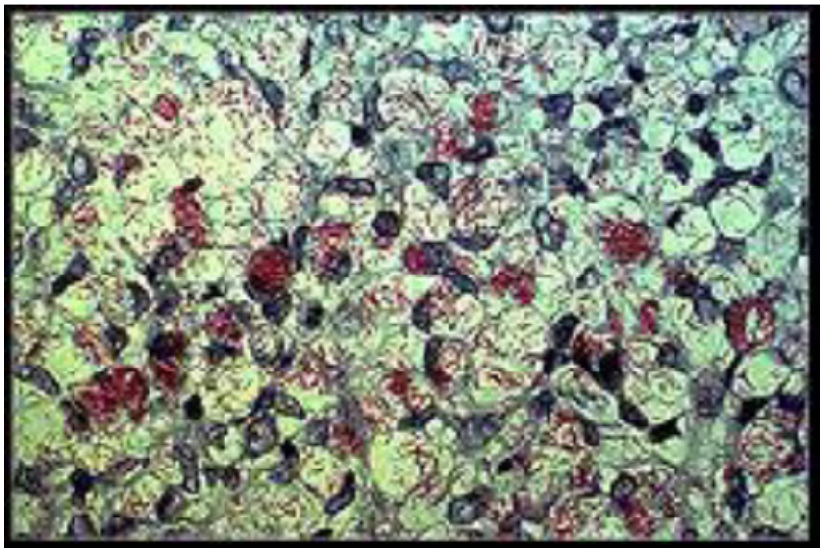

Figure no 1. Mycobacterium lepraein Ziehl-Nielsen1staining

Morbus Hansen's disease has long been known, and has even existed since the days of ancient Egyptian, Indian or Chinese civilizations [1]. Many old myths believe that Morbus Hansen is a curse disease, karma for mistakes in his previous life to genetic diseases. And not infrequently, Morbus Hansen sufferers are alienated from their environment and get social stigma. In fact, Morbus Hansen can be controlled and treated until it heals.

PREVALENCE

Hansen's Morbus disease can occur at any age and children are more susceptible to contracting Mycobacterium leprae infection than adults. This disease is transmitted from one person to another through airborne droplets. The spread of Mycobacterium leprae can

also be influenced by several factors, including socioeconomic status, population density, nutrition, and immune response. The endemicity rate in a region also describes the degree of public health facilities and the BCG immunization attainment rate in a region.

Hansen Morbus is rarely found in very young children because of the long incubation period before the onset of clinical manifestations [1, 3]. Morbus Hansen cases are more common in males than in females. An increase in the incidence of Morbus Hansen occurs in people with household contacts with Morbus Hansen sufferers [3]. The incidence rate is higher in contacts with multibacillary cases (MB) than in pausibacillary (PB) 5-14 times.

Morbus Hansen disease can be found all over the world, but Morbus Hansen is still a health problem in endemic areas, such as Africa, Southeast Asia and Latin America. In certain countries, there are even concentrated groups of Morbus Hansen sufferers, such as in India (more than 1000 colonies with Morbus Hansen sufferers), China, Romania, Egypt, Nepal, Somalia, Liberia, Vietnam, and in Japan [3].

CHARACTERISTIC

Morbus Hansen disease is characterized by a granulomatous inflammatory process in the peripheral nerves and mucosa of the upper respiratory tract and lesions on the skin are the main clinical signs that can be seen [1, 2]. Mycobacterium leprae is intracellular, namely in reticuloendothelial cells, for example macrophages and on peripheral nerves, namely on the Schwan cell. Mycobacterium leprae infection can also attack the eye and testes [10].

The classic clinical signs of Morbus Hansen play an important role in establishing the diagnosis of Morbus Hansen, although the presence of Mycobacterium leprae on skin smears, histopathological features and Polymerase Chain Reaction (PCR) are sometimes needed to assist diagnosis [3]. Morbus Hansen should be suspected in patients with the following signs and symptoms: skin lesions in the form of pale or reddish spots; decrease or loss of sensation in the skin lesions; numbness in the arm or leg; weakness in the arms, legs or eyelids; painful nerves; swelling of the face or earlobes; numb sores on the arms and legs; as well as skin stiffness [3].

The clinical and histopathological features of Morbus Hansen's disease depend on the immunological status of the patient at the time of Mycobacterium leprae infection and according to disease progression. The body's immune response to Mycobacterium leprae

varies and gives a clinical picture those changes spontaneously and is called the Morbus Hansen reaction. This Morbus Hansen reaction is also responsible for the permanent nerve damage and deformity caused by the Mycobacterium leprae infection. This fluctuating immune response is influenced by several things, including: response to Morbus Hansen treatment, stress, and pregnancy.

TRANSMISSION OF MORBUS HANSEN

The transmission of Morbus Hansen is suspected through several mechanisms, including: air droplets, child to parent, parent to child, between siblings, length of exposure to Morbus Hansen patients, genetics and environmental conditions [1]. Mycobacterium leprae infection in Morbus Hansen patients is suspected mainly through respiratory tract, but there is also evidence that Mycobacterium leprae infection can also be through wounds on the skin. The mechanism of how germs spread from the entry site of the germs to the location of the Morbus Hansen lesion is still unclear [3]. The incubation period for Morbus Hansen, namely from infection with the Mycobacterium leprae bacteria until the onset of clinical manifestations is quite long [1, 3, 10].

The incubation period in MH type PB patients is longer short (ie 2-5 years) than in MB type MH patients (between 5 and 10 years, sometimes even longer). Several genes have been studied and are associated with individual susceptibility to infection with the bacteria Mycobacterium leprae. Recent studies have shown that Morbus Hansen patients have defects in the cellular immune response that make them more susceptible to infection with the bacteria Mycobacterium leprae. Approximately 10 percent of the world's population is actually at risk for developing Morbus Hansen disease [12, 13].

CHEMOPROPHYLAXIS IN INDIVIDUALS WHO HAVE CLOSE CONTACT WITH MORBUS HANSEN PATIENTS

Chemoprophylaxis is defined as the administration of drugs, including antibiotics, to prevent infection from developing or progression from infection to manifest disease. Early detection of disease and appropriate treatment using a multidrug therapy (MDT) regimen are the foundation stones of a Morbus disease eradication program. Since the introduction of MDT use in 1981, more than 15 million Morbus Hansen patients worldwide have received

treatment. The use of MDT has also reduced the prevalence rate of Morbus Hansen's disease from 5.2 million patients in the 1980s to about 200 000 patients this decade.

Early detection of cases and appropriate treatment with MDT are still not optimal in eradicating Morbus Hansen's disease [3]. This shows that the case finding rate for new Morbus Hansen cases tends to be constant, namely 200000-250000 cases per year for the past 8 years [4]. There are at least two reasons for this. By the time Morbus Hansen's case was discovered, the incubation period had lasted quite a while, and during the incubation period, the individual could potentially infect many other individuals who came into contact with him. In addition, there is an undetected source of infection. This is reinforced by evidence that there are healthy individuals who are carriers of the Mycobacterium leprae bacteria in the mucosa of the cavity, which allows it to infect other individuals.

Therefore we need a global strategy to break the chain of transmission of Morbus Hansen so that it can reduce the incidence of Morbus Hansen around the world. Therefore, since 2013 WHO has launched a program to optimize the eradication of Morbus Hansen disease which includes the following points: tracking individuals who have contact with the new Morbus Hansen patient accompanied by post-exposure prophylaxis; development of diagnostic tools to identify those at risk of developing new Hansen Morbus sufferers; and early detection of Morbus Hansen and appropriate treatment [4].

Contact with a patient with Morbus Hansen is a risk factor for contracting MH [11]. Individuals who have contact with a patient with a new Morbus Hansen case have a high risk of contacting Mycobacterium leprae infection, and this can be grouped based on the degree of proximity to the Morbus Hansen patient both in terms of closeness, physical and close blood relations (family or relatives, living in the same house, and neighbors) [4].

The Morbus Hansen case early detection program, which includes neighbors who live close to the Morbus Hansen patient with a radius of approximately 200 meters, provides a fairly high detection rate for the new Morbus Hansen case. The discovery rate of new Morbus Hansen cases in family members of Morbus Hansen patients and in neighbors who live close to MH patients gives almost the same results [11]. At least 20-30% of new Morbus Hansen cases are detected in these contact individuals. As for data in Indonesia, around 29.8% of Morbus Hansen cases were only found in individuals who had contact with Morbus Hansen patients [4].

The term chemoprophylaxis has been used frequently since the 1980s [7]. Chemoprophylaxis can be administered to a person at high risk based on an epidemiological risk assessment without knowing whether the person is actually infected. Socioeconomic conditions and nutritional deficiencies are risk factors for Morbus Hansen in general, and also influenced by blood relations with the patient, age of contact, and the number of bacteria in the patient are risk factors associated with clinical Morbus Hansen on contact. Chemoprophylaxis using antibiotics and immunoprophylaxis with BCG vaccination has become one of the efforts to prevent the occurrence of Morbus Hansen in individuals at high risk of exposure to the Mycobacterium leprae bacteria [2-9, 11]. However, until now, neither chemoprophylaxis nor immunoprophylaxis has not been included in the official recommendations issued by WHO for the management of Morbus Hansen cases [8]. Individual tracing of Morbus Hansen patient contacts and chemoprophylaxis has decreased the detection rate of new Morbus Hansen cases in Brazil and the trend continues. It is predicted that Morbus Hansen's disease will be completely eradicated by 2030.

In a study conducted in 2002 (COLEP study) in Bangladesh, there were 1.037 patients enrolled in the study, of which there were 400 patients with single papalibacillary (PB) MH lesions, 342 patients with multiple (2-5) MH pausibacillary (PB) lesions, and 295 patients with multibacillary MH (MB). Each patient was recorded as having 20-30 contacts. These contacts include people who live in the same house or share a kitchen with the patient, who live next door to the patient, and people with social contacts who live in the same room as the patient for at least 4 hours a day for at least 5 days a week.

Ideally, optimal chemoprophylaxis has maximum effectiveness and minimal risk of side effects. Antibiotic candidates for chemoprophylaxis Morbus Hansen should be absorbed orally quickly without having any gastrointestinal interactions, capable of intracellular penetration into tissues infected with Mycobacterium leprae, and eliminated slowly by the body (has a long half-life) so that the effect is long-term and one-time enough regiment [5]. Unfortunately, protection against Morbus Hansen due to chemoprophylaxis only lasts a short time (two to three years) and is less effective in individuals who have had very close contact with the patient Morbus Hansen.

Several antibiotics have been shown to have both bacteriostatic and bactericidal activity against Mycobacterium leprae. Antibiotics such as dapsone, clofazimine, quinolones, minocycline, and macrolides (azithromycin and clarithromycin) were less effective as

chemoprophylaxis in Morbus Hansen. Rifamycin (rifampin and rifapetin) and diarylquinoline (R207910) are two classes of antibiotics that are suitable for chemoprophylaxis Morbus Hansen. An effective chemoprophylactic strategy not only takes into account the choice of drug type, dosage, and frequency of administration, but also the ideal number and type of contact individuals for Morbus Hansen patients who need to be traced, examined and given treatment [4]. Based on observations, the acceptance of individual contacts to the program Chemoprophylaxis is quite good and positive, [14, 15] but the Morbus Hansen disease eradication program still needs to pay attention to the social aspect, namely the social stigma regarding Morbus Hansen. Morbus Hansen patients are still reluctant and afraid to inform openly about the disease they suffer from to others, be it family or neighbors. The effectiveness of giving chemoprophylaxis to contact individuals as well as chemoprophylaxis in mass populations in endemic areas has been evaluated in various studies [14].

DRUG RESISTANCE AND COMBINATION THERAPY

Soon after the emergence of streptomycin as part of therapy for tuberculosis, it was recognized that the tubercular bacillus could become resistant very rapidly, although it continues to be effective against M. tuberculosis. The same thing happened with the use of INH as a single drug. This has led to the understanding that if these drugs are combined, the possibility of drug resistance is reduced. Based on in vitro confirmation and the use of combination drug therapy in cases of tuberculosis that were carried out afterwards, there will indeed be a decrease in the number of drug resistant tuberculosis. However, in leprosy, dapsone and other drugs are used as monotherapy for a long time without such understanding. Although there were several instances where patients receiving dapsone therapy experienced deterioration in their condition, resistance could not be confirmed due to unavailability of facilities. In response to an experiment carried out in 1960 that the sole region of the mouse foot allowed the regular but limited multiplication of M. leprae, patients who worsened during therapy or experienced relapse after discontinuation of dapsone were observed in this study. Pettit and colleagues, using a mouse foot model, were the first group of researchers to demonstrate the emergence of a dapsone-resistant strain of M. leprae. Soon a number of cases of dapsone resistance were reported by other

investigators. Research has confirmed that resistance to dapsone is a global phenomenon and continues to increase [1, 2].

There are two types of drug resistance: (1) Secondary or acquired resistance that arises due to inadequate therapy and is often in the form of irregular monotherapy and gives a clinical effect in the form of an improvement in the condition that appears quickly and is followed by a decline in the condition, although the drug is still being administered; (2) Primary resistance that occurs in untreated patients and infections caused by organisms that are resistant to treatment, are caused by patients who have relapsed with secondary resistance and spread it to the environment [3].

How resistance to M. leprae develops is thought to be due to the selection of mutants that are completely resistant or partially resistant that occurs naturally - a normal phenomenon in any large population of organisms. With single drug administration, susceptible populations will be killed but mutant populations that can survive will continue to multiply, resulting in bacteriological relapse and of course clinical relapse. Unlike some other chemotherapeutic agents, M. leprae's resistance to dapsone is a multi-stage phenomenon. Therefore, all levels or degrees of resistance can be seen. Patients who receive regular therapy in full doses will relapse quite slowly and generally have a high degree of resistance. However, relapses tend to occur more frequently among populations receiving monotherapy, low dose therapy, and /or irregularities [12].

It is thus clear that if dapsone monotherapy is continued, a large proportion of patients will appear to have relapsed with dapsone-resistant bacilli. In line with this, similar problems will arise if other drugs are also given monotherapy. There are a number of reports regarding rifampin resistance, with most of them coming from patients receiving rifampin therapy as a single drug. Resistance to clofazimine has also been confirmed. Monotherapy with thioamide has also been shown to be associated with relapse due to drug resistance. However, the likelihood of spontaneously occurring M. leprae resistance varies with each drug, low with rifampin (about 1 in 109) and relatively more frequent with dapsone (about 1 in 106) [13].

To solve the problem of emerging drug resistance and to provide resistance therapy suspended and unsuspended, bactericidal drugs are recommended for use in combination. This is based on observations made on bacteriological studies of M. tuberculosis and from clinical experience of pulmonary tuberculosis. The rationale for this, where we need to

administer chemotherapeutic drugs in combination, is that organisms that are spontaneously resistant to one drug can be killed using other drugs combined in combination and vice versa. Because the likelihood of spontaneous emergence of mutants resistant to two drugs /due to the selection process is very small, 2 drug combinations are sufficient for most untreated patients infected with bacterial populations that are predominantly drug sensitive. De novo infection with resistant M. leprae bacteria in communities (e.g. primary resistance) is a significant problem. Therefore, if a patient is receiving combination therapy with two drugs with a tendency for a large number of M. leprae bacteria to be primarily resistant to either of these two drugs, then these patients are actually undergoing monotherapy with the other drug and eventually the M. leprae bacteria. The infected patient will become resistant to the second drug as well [14].

In practice, it is not possible to identify who is infected by a population of sensitive or resistant bacteria or what proportion of the population is drug-resistant in total bacterial counts. Therefore, for management purposes it is assumed that each patient, who has a large number of bacilli in his body (MB patient), has a population of resistant organisms and thus needs to be treated using a triple drug combination. On the other hand, patients with negative smear results (PB patients) had only a small population of M. leprae bacilli, which counts to less than one million. Thus the likelihood of PB patients having drug-resistant mutant bacilli arising spontaneously is very small or almost non-existent. That way, the use of combination therapy of two types of drugs can be sure to be sufficient to kill even resistant bacilli even if the patient has a bacterial infection that is resistant to one particular type of drug. Based on all the above considerations, separate regimens to control/eliminate leprosy in multibacillary and pausibacillary patients have been formulated. This will be further elaborated on in the next section [14, 15].

Experience has shown that combination therapy, as used in leprosy and often referred to as MDT, is an effective form of therapy in all cases and has played a role in checking for the emergence of drug resistance. The efficacy of this regimen has been described and no further studies are needed to compare the usefulness of MDT versus placebo as a control. However, whether these regimens are safe and how well they are tolerated by the body is a matter of concern. The global application of MDT, two combination drugs for Paucibacillary patients and three drug regimens for multibacillary cases, has shown that the use of the recommended combination drugs as a whole is very safe and highly acceptable by the body.

Observations in the short and long term to assess the use of three drug combinations that are commonly used, namely rifampin, clofazimine and dapsone; indicates that most of the side effects that appear are minor and temporary. Less than 1% of patients have to stop taking the drug because of side effects and/or discoloration due to clofazimine. Acceptance of the use of clofazimine is quite low among the population with lighter colored skin because of the side effects of using this drug which causes brownish yellow discoloration. Although a number of mutagenic effects on drugs, particularly rifampin, have been observed from in vitro trials using Bacillus subtalis, no problems were seen when this regimen was tested in both animal and human trials. Therefore, MDT administration can be continued even during pregnancy. However, as a safety measure, in the first trimester, it is better to delay the use of rifampin. Continued administration of clofazimine during pregnancy can cause color changes in the baby who is later born. Likewise, excretion of this drug in the breast milk of a nursing mother, who is receiving MDT therapy, can cause discoloration in the baby. Whether the excretion of this drug, either dapsone or clofazimine, in breast milk can provide protection to the baby from infection is still not known, but it is still very likely to happen [15].

DISCUSSION AND CONCLUSION

The Morbus Hansen control program has been quite successful in reducing the incidence of Morbus Hansen disease worldwide since the implementation of the MDT treatment program in Morbus Hansen patients. However, the detection rate of new Morbus Hansen cases, especially in endemic areas, remains high. Therefore, the Morbus Hansen disease eradication program also includes early detection of Morbus Hansen cases in individuals who come into contact with Morbus Hansen patients as well as prophylaxis to prevent the onset of Morbus Hansen disease.

DECLARATION OF COMPETING INTEREST

All authors declare no conflicts of interest.

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