

An Overview Background of Hensen's Disease or Leprosy

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Abstract

Leprosy is a granulomatous disease acquired by the *Mycobacterium leprae*. Although there is a significant improvement in the treatment of this disease, it is still endemic in many regions, commonly in India, Indonesia, Brazil and many other nations. The pathogenesis of the bacteria is full of complexity and it has remained to be elucidated. The clinical presentation of the disease based on the patient's immune system. Surprisingly, leprosy is a type disease which diagnosis can only be processed when one of the clinical signs described by WHO (discussed below) has appeared in infected patients. Like tuberculosis, leprosy is also treated with multidrug therapy. Moreover, the future directions of the leprosy were also discussed in this paper.

Keywords: Hensen's Disease; Leprosy; Tuberculosis

Introduction

Hensen's Disease (HD) or leprosy is a chronic infection disease caused by *Mycobacterium leprae*, which is an obligated intracellular bacillus, identified by Gerhard Henrik Armauer Hansen [1]. The organism predilects for the skin and peripheral nerves. In the skin the bacilli can be found in macrophages and histocytes [2,3], whereas they have an affinity for Schwann cells in peripheral nerves [4]. Moreover, the HD caused by *M. leprae* is leading to severe disabilities and social stigma globally.

The Hensen's disease is still endemic in several areas of the world. This infection is prevalent in more than 15 countries, whereas 83% of the cases were registered in India, Brazil and Birmania. Among those countries, 64% cases were found in India [5,6]. At the beginning of the 90's, the WHO projected the 'final push strategy' for leprosy, with the intention of 'elimination' (reducing the prevalence below 1 case per 10,000 people) in 2000 and it was conquered at the global level [6].

M. leprae is a non-culturable organism because of its prolong incubation period. However, it has been grown in the foot pads of armadillos. Unlike the *Mycobacterium tuberculosis*, the replication of *M. leprae* takes from 11 to 13 days. Moreover, the optimal temperature for *M. leprae* to grow is between 27°C and 30°C. Nevertheless, the infectious disease is curable and treated with multi-drug therapy.

Classification

The primary mode of transmission of *M. leprae* is by aerosol spread of nasal secretions and uptake thorough respiratory mucosa [7]. *M. leprae* directly infects the modulator of innate and adaptive immune response also known as macrophages.

Depending on the patient's immune system and disease dissemination, the HD is categorized into 2 poles representing as tuberculoid leprosy (TL) and lepromatous leprosy (LL) respectively. Additionally, there are indeterminant cases, which are knowns as borderline leprosy or dimorphous. The borderline leprosy is further organized into borderline lepromatous (BL), borderline tuberculoid (BT) and

borderline-borderline (BB) leprosy regarding the poles they tend towards. The dimorphous cases are assumed to characterise the initial stage of the disease and last of all they progress to form lepromatous leprosy [5,6,8].

Tuberculous leprosy is stable, rarely spreadable and self-limiting, while the other one, lepromatous leprosy is at the active, liberal, systemic and infectious end of the spectrum [9]. The tuberculoid patients show a specific immune response to *M. leprae* with Th1 profile, production of IFN- γ and positive Misuda reaction. On the other hand, the lepromatous patients have nearly 1:2 ratio of CD4: CD8 and Th2 profile with high titers of anti-*M. leprae* antibodies. Moreover, skin test indicates negative reaction in the respective patients [10,11].

Besides it, the infected patients were classified into two groups: paucibacillary (TT, BT) and multibacillary (BB, BL, LL) with the aim of treatment [12]. The organisation was made on the basis of number of lesions. If there are less than or equal five lesions on the skin, it is considered as paucibacillary, while the multibacillary is formed when more than five lesions were found.

Genetic factors of host response to *M. leprae*

Various examinations were performed to understand the genetic determinants of host response to progress the disease of leprosy. Previous observations revealed that four pathways along with a prominence of single nucleotide polymorphisms play a crucial role in disease development. The SNP association studies indicated that small amount of lymphotoxin- α (LTA) producing allele serve as the genetic risk factor for initiation of leprosy [13]. Earlier it was found that SNPs are associated with a variety of genes involved in the development of disease or reactions, including vitamin D receptors (VDR), TNF- α , IL-10, IFN- γ , HLA genes and TLR1 [14-17]. On the contrary, linkage studies demonstrated that E3-ubiquitin ligase encode by PARK2 gene and PACRG gene are contributed as a polymorphic risk factors in the promoter area [18]. Due to the presence of higher genetic diversity, it is quite difficult to understand the development of disease. Probably, many unknown risk factors and pathways are still remained to be revealed to fully understand the pathogenicity of Hensen's disease.

Leprosy Reaction

The dysfunction of peripheral nerves in leprosy patients is often triggered by leprosy reactions [5,19]. 30 - 50% of the leprosy infected patients are affected by reactions with a characterization of inflammations which is likely to appear at the beginning of the treatment or during the progression of disease [20]. There are two types of leprosy reaction, namely type 1 or reversal reaction (RRs) and type 2 or Erythema nodosum leprosum (ENL).

Type 1 reaction is normally found in borderline leprosy. Patients with this type of reaction have small number of bacilli together with the lower level of antibody compared to the lepromatous patients [21,22].

Type 1 or reversal reaction is developed by two reasons:

1. Changes in patient's immune system,
2. Antimicrobial drugs treatments that induce the development of cell mediated hypersensitivity mechanism during the beginning months of treatment or after it has stopped [9].

Type 2 reaction or ENL causes cellular dysfunction. It arises in nearly 60% of lepromatous leprosy patients and tend to reappear quite a few times along with the progression of disease [23]. This type of reaction commonly affects the nerves [19,24].

In addition to these two types of reactions, there is also another potential type of leprosy reaction, known as Lucio phenomenon. It is related with diffuse of Lucio and Latapí, which are a form of lepromatous leprosy. This form of disease results in diffuse necrotizing lesions characterized by *M. leprae* or *M. lepromatosis* endothelial cell injury [25].

The predilection of *M. leprae* to peripheral nerve

M. leprae has a predilection for Schwann cells and it activates after the attachment of the bacilli to α 2-laminin and adhesins from the basal lamina and to α -dystroglycan and ErbB2 receptors on its cell surface [26].

Once the *M. leprae* enters to the Schwann cells, it causes the dedifferentiation of the cells into immature cells via the activation of Erk1/2 pathway. This condition helps the bacteria to proliferate [27]. Recent research showed that the dedifferentiation is the root to reprogram the Schwann cell into a 'stem cell-like' cell. The latter one further redifferentiate into mesenchymal cells. The transformed cells are able to alter the macrophage into granulomas that act as a Trojan horse for dissemination of *M. leprae* leading to the spread of infection [2,28].

Diagnosis

HD is diagnosed based on the 3 cardinal signs described by WHO's Expert Committee on Leprosy in 1997 [5,23]. The diagnosis is performed only when the individual has 1 or more of the clinal signs mentioned below:

1. A hypopigmented or erythematous skin lesion with sensory loss
2. A thickened peripheral nerve
3. A positive skin smear or bacilli detected in a biopsy

If all those 3 signs are observed, the sensitivity of diagnosis has been recorded as high as 97% [23].

Smear test

The smear test is performed by collecting the samples from an ear lobe or skin lesions and nasal mucosa. The specificity of this test is 100% while the sensitivity is 50% [29,30]. Like the *M. tuberculosis*, Ziehl-Neelsen stain is used to visualize the acid-fast bacilli.

Skin biopsy

Fite-Faraco staining method is used to screen the bacilli from the skin lesion. The bacteria are not observed at the tuberculoid spectrum, but the granulomas were found along with the nerve involvement. However, an inflammatory infiltrate with Virchow cells provided with bacilli can be visualized in lepromatous leprosy.

Lepromin test

This test utilizes the inactivated *M. leprae* produced from lepromas. 0.1 ml of lepromin is injected in the forearm and the interpretation of the reaction is recorded at 2 instants. The first examination is looked at 24 or 48 hrs for the Fernandez reaction where the cross-reactivity of *M. leprae* with other mycobacteria can be observed. After 21 days of the injection, the latter, Misuda reaction is read and it specifies resistance to the bacteria.

Serology

Phenolic glycolipid 1 (PGL-1) antibody is currently used to examine the bacilli. However, this technique is not very useful in paucibacillary patients [31,32].

Treatment

In 1981, the WHO introduced the first line drugs of rifampicin, clofazimine and dapsone (diaminodiphenyl sulfone) for the treatment of leprosy [33]. As indicated by the physicians, infected individuals should take the combination of these drugs monthly.

There are three solid facts of using multi-drug therapy, which are:

1. To prevent the resistance to dapsone
2. To reduce the infectivity in patients
3. To lower the chance of recurrence and reactions [34].

Apart from the first-line drugs, the second line drugs containing, minocycline, ofloxacin, and clarithromycin are also used. Although the second line drugs are highly dynamic, they are not the first-choice for treatments because of their higher price.

Vaccines

Reorganization of immune system against mycobacterial antigens has a prophylactic impact on the leprosy vaccine. Mycobacterium w introduced by Talwar in 1978; the combination of BCG (Bacillus Calmette- Guerin) with *M. leprae*, called the Convit vaccine proposed in 1992 and Mycobacterium ICRC are some of the vaccines which are in current used. Generally, in some part of the regions, the BCG vaccine is given to those children (under the age of 12 years), who are considered to be in contact with leprosy patients. However, the study revealed that only 50% of the protection against HD were recorded with BCG vaccines [35].

Future Perspective

Although the leprosy is a curable disease, it remains to be an important health issue in various regions of the world. It has an immense effect on the lives of millions of people as well as on their social and economic customs. White and Franco-Paredes (2015) suggested that the corresponded organizations, who have previously worked on leprosy make it acknowledged that leprosy is still a disease of dangers [20]. If the facilities for leprosy or HD control weakens, there is a high chance of re-emergence of leprosy [36]. Therefore, the leprosy disease acquired by *M. leprae* is a pathogen, which cannot be consider as a tamed organism.

It is essential to introduce new and more sensitive diagnostic tools which is able to detect the presence of bacilli before the signs and symptoms have appeared. For example, determination of the antibody to *M. leprae* with the same technique of using PGL-1 antigen, prior to the development of signs and symptoms will be a positive step to control leprosy [20]. Besides, it is important for new diagnostic tools to provide higher sensitivity and specificity.

Next might be having enough funds for HD research which will be useful to elucidate more about the pathogenesis of *M. leprae* both in the cellular and molecular level. If there is a financial support to continue the research only on the complex nature of leprosy will lead to find a way of eradication. Nonetheless, funding for research on leprosy is a significant challenge for future.

Conclusion

Leprosy or HD has a massive impact on societies. There are a lot of challenges encounter in this disease, including its complicated pathogenesis, diagnosis, vaccines as well as its prevention and control. Therefore, many explorations still need to be done to provide knowledge on the mechanism of pathologic, which might helpful in treatment and also in vaccine production. Consequently, in current situation, it is necessary to control the prevalence of leprosy globally.

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