



## **EPIDEMIOLOGY OF HANSEN'S DISEASE AND THE MECHANISM OF NERVE INJURY IN THE DISEASE: A REVIEW**

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### **ABSTRACT**

Leprosy, a chronic infectious disease affecting mainly the peripheral nerves and the skin, has varied degree of endemism along the globe. While there are countries with registered prevalence less than 1 per 10,000 people, there still are places that have not achieved this elimination status yet. A number of environmental, social, economical, and cultural factors contribute to the transmission of this disease. The disease presents in a wide variety of ways as the mechanisms of nerve injury in it is a complex and multifaceted pattern.

**Keywords:** Leprosy; epidemiology; transmission; nerve injury

## INTRODUCTION

Hansen's disease (HD) or leprosy is a chronic infectious disease caused by *Mycobacterium leprae* that affects predominantly the skin and the peripheral nerves but also may affect the mucosa of the upper respiratory tract and the eyes and other tissues such as bones and some viscera. It is one of the ancient diseases known holding so many challenges that are yet to be accomplished. Its history is dated about 4000 years back where they described it to be caused by *M. leprae* bacilli in the books from Old World in India [1]. The disease is named after a Norwegian physician Gerhard Armauer Hansen who identified the causative bacillus in 1873 [2]. While the disease has been studied so many times in the literature, its pathophysiology still remains complicated and discussing it is a crucial step towards the diagnosis, treatment and control of the disease. Our study hereby contains the detailed mechanism of nerve injury that take place in the process of the disease.

## DISCUSSION

### **Epidemiology:**

HD is prevalent in the tropical countries, mainly those that are developing or underdeveloped. With the success of MDT introduced approximately three decades back in the 1980s, the worldwide burden of leprosy has significantly reduced. Elimination of HD as a public health problem (defined as the prevalence lower than 1 case per 10,000 inhabitants) was achieved globally in 2000 and in most countries by 2005. But still, the worldwide registered prevalence of leprosy at the end of 2015 (reported by 138 countries) was 176,176 cases (0.18 cases per 10 000 people) and the number of new cases reported was 211,973 (0.21 new cases per 10 000 people) [www.who.int]. About 105 countries situated in Southeast Asia, America, Africa, Eastern Mediterranean and Western Pacific Region (WPR), contribute to a large part of this concentration [1,2].

India ranks first in terms of holding absolute number of leprosy cases (attributing 60% of the global new leprosy cases) with Brazil ranking second (13% of the global new cases) that has not yet achieved the goal of leprosy elimination and Indonesia ranking third (8 % of total global new cases). Other countries that comprise of new cases between 1000 and 10000 include from AFR, the Democratic Republic of Congo, Ethiopia, Madagascar, Mozambique, Nigeria and United Republic of Tanzania; from SEAR, Bangladesh, Myanmar, Nepal and Sri Lanka; and from WPR, the Philippines. The proportion of female among the new cases in 2015 globally was 38.8% with the highest number being 49.2% from Burkina Faso in AFR. Globally the proportion of child cases in 2015 was 8.9%, the highest number being reported in Comoros in AFR (38.1%) [2,3].

Though HD is primarily caused by the infection with the bacillus *M. leprae*, many entities have been known to affect the transmission of the disease and its control. They include various social, environmental and economic factors. This has been discussed in many literatures in the history as well.

Leprosy is found to be more prevalent among people with darker skin color and those residing at tropical areas. People indulged in occupations with higher environmental exposure such as agriculture and lower education level are more susceptible to get infected with this disease. Likewise, the direct proportional link of poverty and leprosy incidence has been discussed before too. The infrastructural development and the sanitary hygiene of a place also determine the risk of transmission of leprosy [4,5,6,7,8,9, 10,11,12,13].

### **Mechanism of nerve injury in Hansen's disease:**

Once any person gets infected with the mycobacterium, the average period of incubation is two to three years and ranging from 6 months to 40 years or longer. The first sign of the disease in more than 90 percent of the patients is a feeling of numbness that may precede skin lesions by a number of years. The first sensation to be lost is the temperature, followed by light touch, pain and then deep pressure. Sensory loss usually begins in the extremities (toes and fingertips).

The most common presentation of leprosy is mononeuritis and the nerves in the upper limbs are affected more often than those of the lower limbs, with the most commonly involved nerves being the ulnar, median, posterior auricular, superficial radial, common fibular, superficial fibular and posterior tibial. However, mononeuritis multiplex, which is involvement of multiple unrelated and distant nerve trunks is also observed. In few cases, nerve damage is a gradually progressive sensorimotor polyneuropathy due to a mononeuritis multiplex summation that can be symmetrical or asymmetrical. The pathogenesis of nerve injury in leprosy can basically be divided into these major events: localization of *M. leprae* into nerves, infection of Schwann cells and dissemination of *M. leprae*, axonal degeneration and demyelination; and immunohistochemical alterations in the nerves [14].

### **Localization of *M. leprae* into nerves:**

Peripheral nervous system (PNS), especially the Schwann cells of myelinated and unmyelinated axons are the target sites of *M. leprae*. They are also present within perineurial cells, smooth muscles, hepatocytes, and endothelial cells of blood vessels in lesser quantity but they do not cause toxic injury to these residing cells. They prefer the cooler areas of the body where they can multiply as the viability of *M. leprae* is greater at 33°C than at 37°C, and the inflammatory cells associated with them can be seen mostly in nerve trunks that are in close proximity to the skin. Therefore, the pattern of sensory loss in leprosy is widely varied and a 'stocking-glove' type of anesthesia is seen in the lepromatous form of leprosy. Two mechanisms have been proposed for the route of entry of *M. leprae* into the peripheral nerves: a direct entry to terminal nerves and a vascular route leading to intraneural infection. The bacilli then bind to the exposed Schwann cells in the dermis via skin abrasions and ascend directly from cutaneous nerves to the mixed sensory and motor nerve fibers trunks. The endothelial cells of blood vessels serve as recess for the bacterium to enter the intraneural compartment [15].

### **Schwann cell infection and dissemination of *M. leprae*:**

Once the *M. leprae* bacilli approach the Schwann cells, they bind to the G domain of the laminin alpha-2 chain expressed on the surface of the Schwann cell-axon unit. This is done via the receptor on *M. leprae* that is a 21kDa histone-like protein called LBP21, coded by the *ML1683* gene [16]. The bacterium then starts the Schwann cell invasion. Once the Schwann cells engulf the bacilli, they proliferate there, as the environment within is favorable for their multiplication. They alter the interior milieu of the Schwann cell, including the changes in Schwann cell expression of a number of genes like glial fibrillary acidic protein, transforming growth factor  $\beta$ 1, NCAM, ICAM, N-cadherin, and L1. These alterations then produce metabolic and functional changes that trigger the immune system in recruiting cytotoxic cells as T lymphocytes and macrophages [17].

### **Axonal atrophy and demyelination:**

The mechanisms of axonal degeneration are different for the lepromatous and the tuberculoid forms of leprosy. One of the important functions of the Schwann cell is to synthesize the myelin sheath around axons. Once these cells are infected by *M. leprae*, it induces demyelination via direct bacterial ligation and activation of the ErbB2 receptor of Neuregulin-1 that regulates normal myelination. So finally all individual axons in nerve bundles undergo segmental demyelination which is seen in early nerve lesions even in the absence of both inflammatory cells and morphologically definable *Mycobacterium leprae*. So either humoral factors or the continued presence of *M. leprae* antigens is thought to be involved in leprosy neuropathy. In established tuberculoid (TT) or borderline tuberculoid (BT) leprosy nerve lesions, an epithelioid cell granuloma with lymphocyte infiltration is seen which eventually destroys the nerve. Axonal degeneration is prominent. Whatever the mechanism of injury occurs during infection with the bacterium, the final common pathway of nerve damage is segmental demyelination. The histological picture of these nerves is quite similar to that of delayed type hypersensitivity. Complement activation and specifically the membrane attack complex (MAC) deposition functions as a disease modifier during the early events of leprosy nerve damage. Complement activation results in the cleavage of C3 and then C5 forming MAC, which causes perforation of eukaryotic cell membranes and lysis of the target cell. Hence MAC deposition has been observed as a cause of nerve damage of lepromatous, but not tuberculoid patients [18].

### **Alterations in the immunohistochemical profile in the distal sensory and autonomic nerves:**

Destruction of cutaneous nerves is presented as significant skin lesions in leprosy. At an early stage of infection, there is a decrease of substances P and CGRP in central and peripheral projections of sensory neurons and is thought to be associated with sensory nociception [19]. Some of the clinical features of

autonomic dysfunctions in lepromatous patients include anhydrosis, denervation of the iris and miotic pupil in the eye. There is an absence of protein gene product, a pan axonal marker, in the small nerves of the ciliary body, the scleral nerves, and the posterior ciliary nerves adjacent to the optic nerve in enucleated lepromatous eyes. This phenomenon is similar to the 'glove and stocking' type of anesthesia seen in lepromatous patients where a symmetrical loss of sensation in all four limbs due to an ascending polyneuritis of the extremities is seen [20].

## CONCLUSION

While having discussed and reviewed the various epidemiological factors, the different possible transmission causes of leprosy and the vivid mechanisms of nerve injury in it, diagnosing leprosy and identifying the sequence in mechanisms of nerve injury challenging because *M. leprae* can present in a number of typical and atypical ways as it is dormant and also undergoes a long incubation period before producing any nerve damage. But millions of advances have been made and still being undertaken in the fields of leprosy diagnosis and management, which leaves us with hopes towards the achievement of some success in this difficult journey of leprosy elimination.

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