Neuropathophysiology in Morbus Hansen or Hansen's Disease: Mechanisms of Nerve Injury

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1 Nose and Skin

Morbus Hansen (MH) is caused by *Mycobacterium (M). leprae* and *M. lepromatosis*. The infection is believed to be acquired through the nasal mucosa and/or small skin injuries. When the infection with live, dead, or fragmented bacilli has entered, these bacilli come in blood and lymph where they are phagocytosed by macrophages. *M. leprae* bacilli can multiply in these macrophages and other phagocytic cells (Schwann cells), at least in those individuals whose host cells can be turned on to support *M. leprae* bacilli [1].

When the antigens circulate in blood and lymph, they are exposed to the immune system. Together with the innate, both the humeral and the cellular adaptive immune system will respond, whether the host will develop "MH" or not.

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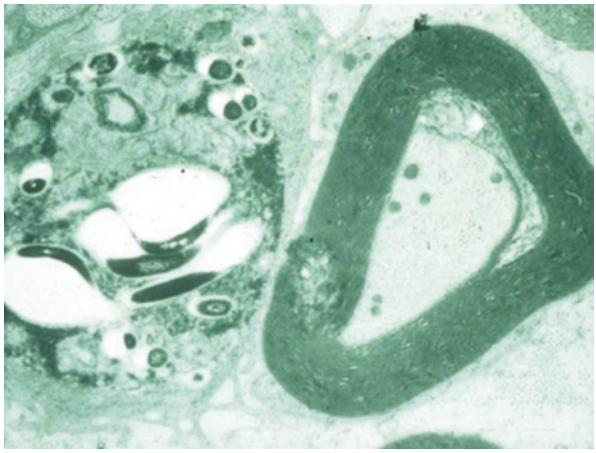

Fig. 1 A macrophage with *M. leprae* in contact with the myeline sheath (Courtesy John Stanley)

2 The Nerve

M. leprae has a predilection for Schwann cells and macrophages in the skin and peripheral nerves. The bacilli survive and multiply in places with a relatively low temperature (32–35 °C). It is difficult for the bacilli to enter the nerve fibres because there are no lymph vessels in the endoneurium. They must enter through the bloodstream and pass the so-called blood–nerve barrier. Graham Weddell observed that MH-related damage occurred at locations where there is movement, for example, the wrist, elbow, knee, and ankle (personal communication). Nerves move there against bone or tunnel wall, such movements cause friction and lead to microtraumata triggering an reparation response.

The endothelial cells of the blood vessels in the endoneurium then express adhesion molecules [2]. Macrophages, some loaded with *M. leprae* antigens will adhere to the endothelial cells and enter via diapedesis into the endoneurium, where they encounter the Schwann cells (Fig. 1). *M. leprae* then invades the Schwann cells as suggested by Anura Rambukkana, using PGL-1 and other surface molecules, leading to proliferation and/or demyelination [3].

3 Damage due to *M. Leprae* Antigens

It is shown that PGL-1 alone, expressed by macrophages, can cause demyelination [4]. Nawal Bahia El Idrissi, et al. showed that another important *M. leprae* surface antigen, lipoarabinomannan, can cause demyelination by complement activation (membrane attack complex (MAC)) [5]. These findings suggest that the presence of antigens alone, without live bacilli, might be a sufficient cause for segmental demyelination, which is the hallmark of MH.

It is important to note that PGL-1 is broken down relatively quickly, whereas lipoarabinomannan may be present for years and may continue to cause damage [6].

Similarly, Toll-like receptors on the Schwann cells such as TLR9, which binds to circulating DNA, and TLR1, 2 and 4, which bind to mycobacterial antigens, maybe a persistent cause of MH-related pathology [7]. This could explain why MH contacts can develop damage without having MH as actual disease [8].

4 Nerve Damage due to Reactions

Most of the MH-related damage occurs during reactions, episodes of exacerbated inflammation in the chronic phase of the infection when there is an increase in immune reactivity. Cell-Mediated Immunity (CMI) at the tuberculoid pole (Th1 response) Type−1-MH Reaction (T-1-MHR) as opposed to the humeral (Th2 response) Type-2-MH Reaction (T-2-MHR) at the lepromatous pole [9, 10].

Nerve damage may occur at three levels:

1. at the skin where the nerve endings are affected
2. at the subcutaneous nerves
3. at the nerve trunks

4.1 In the Skin

The histopathology of reactional tuberculoid MH [11] shows granuloma formation high in the dermis and dermal papillae. This infiltrate may erode the epidermis and destroys the nerve endings in the papillae. It is not unlikely that the driving force behind these damaging reactions is antigenic determinants in the epidermis and in the nerve endings, which are identical to those of *M. leprae* (antigenic mimicry). This reaction could be an autoimmune phenomenon (Fig. 2) [12].

In borderline MH, the nerves of the lower dermis and especially those located around the adnexa are most often involved. Granuloma formation can be seen in and

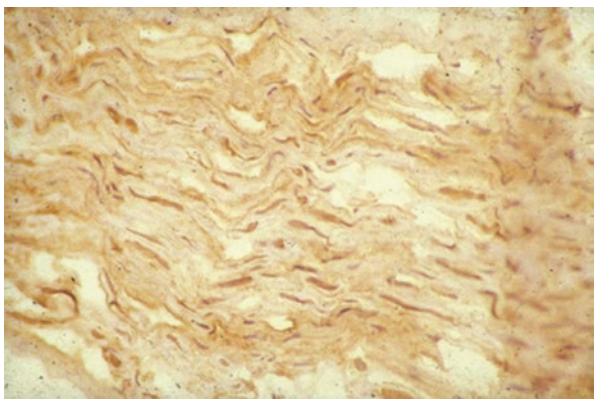

Fig. 2 A normal nerve stained with monoclonal antibodies against *M. lepra* (Courtesy Ben Naafs)

around these nerves together with a proliferation of Schwann cells in and around the perineurium. Damage can be attributed to compression and destruction of the nerve fibres by the epithelioid granuloma. During the reactional episode, there is an influx of immunocompetent cells with oedema formation and expanding granuloma. This contributes to further nerve damage, especially when extracellular oedema accumulates inside the thickened neural sheaths, converting it into a rigid tube compromising the axons inside [13].

4.2 In Large Subcutaneous Nerves and Nerve Trunks

The mechanisms that occur here are more complicated. At the tuberculoid end of the spectrum, these processes are like those in the skin, with massive granuloma formation with occasional colliquation and abscess formation. Further into the borderline range, these features are usually less distinct and often even absent. Frequently only oedema is observed [13].

Damage to cutaneous and subcutaneous nerves causes loss of sensation in the affected areas and loss of autonomic nerve function like sweating and regulation of vascular tone. However, it is the damage to the peripheral nerve trunks which is the major consequence of reactions. This damage is partly caused by the immune system, but mechanical factors are also involved [13] (Fig. 3). During a T-1-MHR (increased CMI), inflammation and consequently oedema occurs in the nerve. The reaction leads to oedema located within the interstitial tissues of the epi-, peri-, and

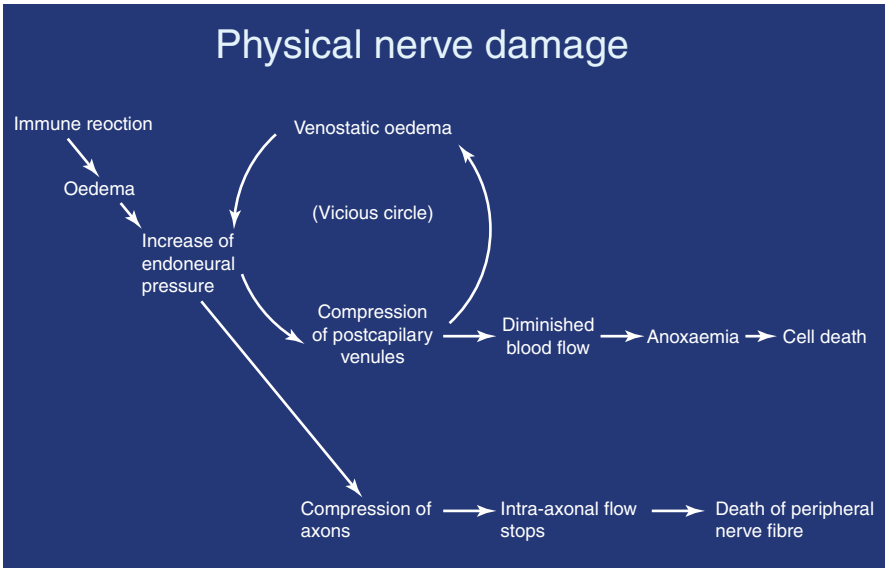

Fig. 3 Immune damage leading to physical damage (Courtesy Ben Naafs)

endoneurium. Unlike the skin, the nerve cannot expand much, limited by its sheaths. The perineurium, which is largely impermeable to fluids, forms a rigid compressing tube around the expanding endoneurium. This results in an increase in pressure within the nerve. As a result, the axons in the endoneurium are compressed by the increased pressure and stop conducting leading to loss of muscular strength, sensation, and autonomic functions (Fig. 3). The intra-axonal flow which brings nutrients from the cell body to the peripheral nerve ending is interrupted, and sooner or later the nerve fibre dies and is destroyed [14].

When the pressure on and the tension along the perineurium increase due to the increase of the pressure in the endoneurium, there is an increase in the pressure on the blood vessels, which transverse obliquely through the perineurium. These blood vessels then become compressed, the venules with relatively low pressure more than the arterioles with higher pressure. The compression of the venules will lead to higher pressure in the capillaries of the endoneurium, which may start "leaking" and thus increase the pressure in the endoneurium. This "venostatic oedema" can maintain itself even when the immunological events subside [14] (Figs. 3 and 4).

In T-2-MHR, the mechanisms leading to tissue destruction, i.e. activation of granulocytes, contribute to damage of nerves fibres and endings. It also has been shown that the cytokines involved are able to demyelinise the nerve fibres. Demyelination seems to be the major nerve damage in multibacillary MH as shown by nerve conduction studies. The damage in multibacillary leprosy may also be caused by lipoarabinomannan that on its own can lead to demyelination by complement activation and MAC formation when in contact with the Schwann cells [5]. Moreover, in the large nerve trunks, the immunological processes may give rise to venostatic oedema with compression of axons similar as described for T-1-MHR.

A recent report may support parts of the above-presented theories: "We observed that viable and dead bacteria distinctly modulate Schwann cell genes, with emphasis to viable bacilli upregulating transcripts related to glial cell plasticity, dedifferentiation and anti-inflammatory profile, while dead bacteria affected genes involved

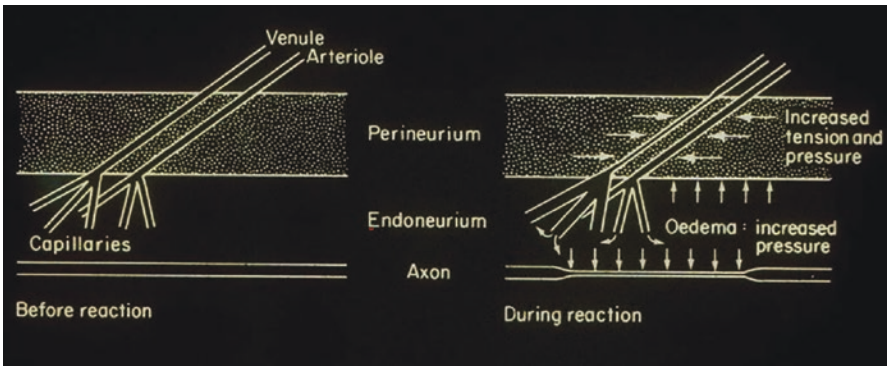

Fig. 4 The pressure on the perineurium compresses the venules more than arterioles which both pass obliquely through the perineurium because the pressure in the venules is lower (Courtesy Ben Naafs)

in neuropathy and pro-inflammatory response. In addition, dead bacteria also upregulated genes associated with nerve support, which expression profile was similar to those obtained from leprosy nerve biopsies. These findings suggest that early exposure to viable and dead bacteria may provoke Schwann cells to behave differentially, with far-reaching implications for the ongoing neuropathy seen in leprosy patients, where a mixture of active and non-active bacteria are found in the nerve microenvironment" [15].

After all these occurrences, the nerve may end as a fibrotic string and the patient is severely disabled. With the knowledge available this can be prevented, provided there are clinicians to diagnose the disease and complications in time and provide proper treatment.

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