Functional impairment of skin appendages due to peripheral nerve involvement by *Mycobacterium leprae*

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Author contributions

DLG and TSL cared for the patient in Figures 1 and 3. DLG and HR-S cared for the patient in Figure 2. DLG and RATS cared for the patients in Figures 4, 5, and 6. SRF interpreted the histology shown in Figure 1 and provided dermatological guidance for the manuscript and photos. DLG wrote the manuscript, which was reviewed, edited and approved by SRF, HR-S and TSL. RATS expired in 2018.
Abstract

In the earliest stage of *Mycobacterium leprae* infection bacteria parasitize fine fiber twigs of autonomic peripheral nerves supplying efferent impulses to appendages of the skin. This obligate intracellular pathogen invades Schwann cells, the glial cells of peripheral nerves. Intracellular events inhibit Schwann cell physiology in complex ways which include demyelination and dedifferentiation. Ultimately axons embraced by their surrounding dysfunctional glia are damaged by poorly understood mechanisms. Loss of nerve conduction impairs the functions of skin appendages including hair growth, sebaceous gland secretion, sweating, and skin pigmentation. At the clinical level these changes may be subtle and may precede the more obvious anesthetic skin lesions associated with Hansen’s disease. Recognizing the early signs of skin appendage malfunction may aid in diagnosis leading to initiation of antimycobacterial treatment. Effective therapy administered early during infection may prevent irreversible peripheral nerve destruction, the presage for morbid complications of leprosy.

**Keywords:** Skin appendages, Hansen’s disease, leprosy, peripheral nervous system, neuropathy
Background

The paramount feature of Hansen’s disease (HD), the eponymic name for leprosy, is the presence of skin lesions which are pleomorphic and anesthetic. Tropism of *Mycobacterium leprae* for sensory, motor, and autonomic cutaneous nerves underlies the unique pathogenesis of infection.\(^1\) Involvement of terminal fine fiber nerve twigs is the earliest histological finding in the disease (Figure 1).\(^2\) Loss of nerve conduction is the ultimate outcome.

Studies on the pathogenesis of HD peripheral neuropathy have shown that *M. leprae* invasion of Schwann cells, the glial cells of the peripheral nervous system, leads to nerve damage.\(^3,4\) For large diameter axons, parasitism of Schwann cells causes demyelination.\(^5,6\) Furthermore, in both large diameter and small diameter unmyelinated axons, neural transmission is lost through re-programming Schwann cells to a dedifferentiated state undermining their normal function to preserve axonal action potentials.\(^5,7\) Investigation into the pathogenesis of neuropathy has shown that immunopathology is likely involved in tuberculoid (paucibacillary) HD by mechanisms in which immune responses directed at *M. leprae* lead to nerve damage.\(^8\)\(^-\)\(^10\) Cell-mediated immunity contributes to neuropathy by cytotoxicity involving T cells and macrophages.\(^11\)\(^-\)\(^13\) Neurotrophins including nerve growth factor produced by neurons and Schwann cells may participate in modulating local immune responses affecting nociceptive fibers.\(^14\) In addition, an *M. leprae* lipoprotein signaling through toll-like receptor 2 (TLR2) expressed on Schwann cell membranes induces apoptosis.\(^15\)

In lepromatous (multibacillary) HD immune responses are suppressed yet nerve damage is prevalent across the spectrum of disease. Recent studies have employed an *ex vivo*
coculture model where purified rodent Schwann cells and purified dorsal root ganglia assemble 1:1 and exhibit morphology identical to the Schwann cell-axon unit of the peripheral nervous system (see reference for recent detailed review). A cell wall localized *M. leprae* phenolic glycolipid found in no other bacteria acts as a ligand to bind the pathogen to the basal lamina surrounding Schwann cells which in turn circumferentially surround axons. Binding occurs preferentially to specific laminin globular modules explaining exclusive tropism of the organism for the basal lamina of Schwann cells. Laminin-bound bacteria find access to Schwann cells by binding to dystroglycan, an integral membrane heterodimeric protein. *M. leprae* interaction with dystroglycan requires laminin suggesting that laminin bridges the bacterium to the Schwann cell membrane through specific molecular interactions. Through these events *M. leprae* is internalized into Schwann cells thus attaining its intracellular location necessary for replication. In addition, the *M. leprae*-laminin-dystrophin complex activates a Schwann cell tyrosine kinase pathway coopting a normal cell signaling pathway. Signal activation leads to a cellular reparative program which is believed to initiate demyelination and dedifferentiation-proliferation functions associated with nerve cell injury. In small diameter non-myelinated axons re-programing of surrounding Schwann cells to a dedifferentiated phenotype may interfere with nerve conduction through as yet unknown mechanisms. Such events underlie the basis for autonomic peripheral neuropathy characteristic of HD. Experiments with immunodeficient mice show that nerve cell demyelination occurs in the absence of innate and acquired cell-mediated immunity. In summary *M. leprae*’s specific tropism for adult peripheral nerve Schwann cells, which provide a niche for intracellular replication, and whose physiological functions are required to preserve axonal nerve transmission, is key to
understanding the pathogenesis in HD. Parasitism of nerve cell bodies or their axons by *M. leprae* is rare.  

Efferent transmission in cutaneous peripheral nerves governs physiological functions of the skin appendages (hair follicles, sebaceous glands, sweat glands and melanizing apparatus for skin pigmentation). Thus, not surprisingly skin appendage physiology may be impaired in HD. Such effects may lead to subtle physical findings, which may be less appreciated by clinicians inexperienced with HD when it presents in non-endemic locales. Although formal studies have not been conducted, we believe that early signs of infection may be revealed by loss of skin appendage function. Failure to appreciate these signs may delay diagnosis and treatment thereby losing the opportunity to prevent irreversible nerve damage. Here we present teaching cases which illustrate dermatological findings due to loss of skin appendage functions during infection with *M. leprae*.

**Case Descriptions and Discussion**

The patients were seen in our clinics and in a leprosarium in Tanzania. By the time we saw them, when the photographs were taken, each had confirmed HD by clinical, histological and microbiological (acid-fast tissue staining) criteria. The findings we describe may or may not have been present as their initial complaint. We discuss the pathogenesis of skin appendage malfunction in each case.

**Case 1.** The patient is a 22-year old immigrant from rural Mexico who was referred to Dermatology Clinic with suspected giant urticaria. His medication history was negative. Multiple erythematous indurated truncal and forehead lesions were outlined but their borders did not change after 3 days. Left eyebrow alopecia was noted (Figure 2). Skin
biopsy was performed which was characteristic for multibacillary HD. Shortly after initiating treatment he returned to his country and was lost to follow-up.

**Comment.** Loss of eyebrow hair results from autonomic denervation of hair follicles (pilosebaceous unit). Left untreated complete loss of eyebrows and eye lashes may occur, a condition known as madarosis. The sympathetic cholinergic (a notable exception to the usual adrenergic neurotransmission) small diameter fibers are particularly susceptible to inhibition in HD.\(^{25}\) Recent research shows that nerve-dependent centripetal smooth muscle contraction of the dermal sheath is required for regressed hair follicle traverse to reach the stem cell reservoir required for new hair growth.\(^{26}\) In addition, loss of sympathetic nerve efferent impulses leads to depletion of hair follicle stem cells.\(^{27}\) Both mechanisms prevent new hair growth as older hair is lost due to natural attrition.

**Case 2.** This 27-year old former missionary was referred to clinic for suspected relapsing HD. He contracted HD while serving in Micronesia and was treated for one year for paucibacillary disease. Complete remission was obtained. Two years after completing treatment he developed skin lesions which were similar to his initial presentation and he sought medical attention. He was on no medications. On examination he appeared healthy except that he had multiple discrete patches which were dry, scaling and hairless (Figure 3). [The photograph was taken during the arid winter season in the Rocky Mountains.] Skin biopsy was performed which confirmed relapsing HD (Figure 1). Because of relapse he was referred to the Long Hansen’s Disease Center in Carville, Louisiana where multibacillary disease was diagnosed and treatment was begun. At last follow-up he had improved considerably and had moved to another city.
Comment. Sebaceous glands largely present in hair follicles make up pilosebaceous units throughout human skin excepting palms and soles. Complex lipid secretions help smooth, lubricate and maintain hydration of the skin. As with hair generation, sebaceous gland secretions require autonomic innervation by the small fiber cholinergic sympathetic nerves. When pilosebaceous gland functions are impaired, dry scaling hairless patches result.

Case 3. This young male patient from the leprosarium in tropical Dar es Salaam, Tanzania had been under treatment for several months for multibacillary HD. Anti-leprosy medications were his only drugs. During the extremely hot, humid “dry season” he complained of heat intolerance. Anhidrosis was noted in discrete geographical areas of his trunk and extremities (Figure 4). These symptoms did not improve with treatment.

Comment. Both types of sweat glands (eccrine and apocrine) are served by parasympathetic cholinergic nerves. Denervation of eccrine sweat glands blocks sudomotor function resulting in focal anhidrosis. Extensive involvement may impair thermoregulation which in turn affects exercise ability especially in tropical climates. Apocrine sweat glands, possibly vestigial in humans, are confined primarily to the axillae and perineum. These are unaffected in HD likely because higher body temperature at these anatomical sites restricts replication of M. leprae, which is notably intolerant to growth at core body temperature.

Case 4. The patient was referred to Dermatology Clinic at Muhimbili National Hospital in Dar es Salaam, TZ. His home was in western Tanzania near Lake Tanganyika. He complained of patches of light-colored skin which were treated topically with anti-fungal medication, but without improvement. He was on no other medications. On examination he appeared
healthy. Depigmented patches were noted to be anesthetic to light touch and pain ruling-out tinea versicolor (Figure 5). He was diagnosed with borderline lepromatous HD.

Comment. Skin pigmentation (melanization) is a complex process controlled by endocrine, paracrine and autocrine physiologies. Anatomical nerve connections to the melanizing apparatus in the epidermis are not yet known but skin pigmentation and disorders of skin pigmentation are almost certainly related to peripheral sensory and autonomic nerve function. Mechanisms affecting melanization can be traced to secretion of neuropeptides from peripheral nerve endings. The melanocortins, e.g. melanocyte stimulating hormone, and the beta-endorphins are implicated in controlling skin pigmentation by modulating melanin synthesis in epidermal melanocytes. These same neuropeptides also appear to control the rate of transfer of melanosomes from melanocytes to keratinocytes, a necessary step for darkening of the skin. Thus, peripheral nerve efferent activity is required for skin melanization and is dependent upon the most superficial small cutaneous nerve fibers penetrating close to epidermal melanocytes. These nerves are preferentially involved by M. leprae due to their proximal location to the cooler ambient temperature of the epidermis. Hypopigmented patches are presumed to be caused by local denervation of superficial nerve twigs required for melanizing physiology as described above.

Case 5. The patient is a middle-aged woman from a mountainous village in Tanzania who was under treatment for lepromatous HD at the Leprosarium hospital in Dar es Salaam. She presented with “humped-up” indurated plaques teaming with acid-fast bacilli (Figure 6). She was treated with dapsone, clofazimine and rifampin complicated by several reversal reactions which were managed with prednisone. No further information was available.
Comment. Increased melanization of HD skin lesions may occur due to treatment. In the case of clofazimine initial treatment causes the lesions to become red, then brown and ultimately exhibit a blue-black hue during long-term therapy. With dapsone therapy a fixed drug eruption may appear as hyperpigmented or black macules. Neither of these drug reactions seem likely in this patient. The mechanism for hyperpigmented lesions in this case is likely unrelated to peripheral nerve involvement. Hyperpigmentation is induced by proopiomelanocortin-derived peptides synthesized in the pituitary gland (humoral effect) and locally in epidermal keratinocytes.\textsuperscript{38} Interleukins and lipid mediators of inflammation (prostaglandins and leukotrienes) promote pigmentation in areas of the skin perturbed by injurious stimuli.\textsuperscript{39} These systemic and local responses may contribute to the hyperpigmentation of HD skin lesions like those shown in Figure 6.

Conclusion

Cutaneous nerve fibers are principally sensory. An additional complement of efferent autonomic nerve fibers accompanies the sensory components. In contrast to sensory nerves, autonomic nerves never innervate the epidermis in mammals. Cutaneous autonomic nerves are sympathetic but employ largely cholinergic neurotransmission. These autonomic efferents govern physiological functions of the skin appendages. \textit{M. leprae} infection inhibits autonomic nerve transmission by parasitism of Schwann cells which surround autonomic non-myelinated small diameter nerve fibers. In patients from endemic regions of the world recognition of the loss of function of any of the skin appendages in a patchy distribution should alert the clinician to the possibility of HD.
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Conflicts of Interest

All authors declare no conflicts of interest for any financial interests or connections, direct or indirect, or other situations that might raise the question of bias for the work presented here.

Patient Consent Statement

Consent to photograph and publish the photos was obtained from all five patients. The Article type (“ID Teaching Cases”) did not require formal approval by Ethics Committees. Likewise formal participant Consent Forms were not required.

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Figure Legends

Figure 1. Histopathology of dermal nerve twig involvement with *Mycobacterium leprae*

Fite-Faraco (original magnification 1000x) acid-fast stain of skin biopsy from lesion of Case 2 shown in Figure 3. Arrowheads mark the borders of a cutaneous nerve twig. Arrows point to acid-fast bacilli partitioning into lipid-rich nerve sheath, a microscopic finding diagnostic for infection by *Mycobacterium leprae*. Asterisks denote surrounding histiocytes, an expected cellular response to infection with this organism.

Figure 2. Focal area of eyebrow alopecia due to impaired new hair growth

Arrow points to focal area of left eyebrow hair loss. Asterisks mark subtle erythematous slightly raised lesions on the forehead. One of these on the left forehead extends into the area of the eyebrow (not well captured in the photo), where partial hair loss is evident. This can progress to complete loss of eyebrow and eyelid hair, a condition known as madarosis.

Figure 3. Xerodermatous lesions resulting from denervation of pilosebaceous units

Scaling, dry hairless lesions on the anterior left leg. Photograph of the patient was taken during winter season in cold, arid climate conditions. Biopsy from one of the lesions is shown in Figure 1.

Figure 4. Eccrine sweat gland involvement

Anhidrosis is evident especially over right scapular and triceps areas. Uninvolved skin shows beads of sweat. The photograph was taken in a tropical climate at ambient temperature approximately 34°C. Note hypopigmentation of anhidrotic skin.
Figure 5. **Hypopigmentation in areas of cutaneous nerve involvement**

Large and small areas of geographical macular hypomelanization are seen on the trunk. The lesions can be distinguished from tinea versicolor by testing for anesthesia to light touch and temperature/pain sensation. Loss of neuropeptide secretions from locally involved cutaneous nerves may explain the inhibition of melanization in affected areas of skin.

Figure 6. **Hyperpigmented flank lesions in a woman with multibacillary leprosy.**

Hyperpigmented, indurated plaques are seen on the right flank. Increased melanization may occur as a result of drug treatment or intralesional induction of melanin synthesis by inflammatory mediators which stimulate proopiomelanocortin-derived peptides (see text for explanation).
