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ID TEACHING CASES

Functional Impairment of Skin Appendages Due to Peripheral Nerve Involvement by *Mycobacterium leprae*

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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. Hansen's disease; leprosy; neuropathy; peripheral nervous system; skin appendages.

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 reprogramming 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 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 used an ex vivo coculture model in which 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) [16]. 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 [4, 17, 18]. Binding occurs preferentially to specific laminin globular modules, explaining exclusive tropism of the organism for the basal lamina of Schwann cells [19, 20]. Laminin-bound bacteria find access to Schwann cells by binding to dystroglycan, an integral membrane heterodimeric protein [21]. *Mycobacterium 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 [5, 7]. Signal activation leads to a cellular reparative program, which is believed to initiate demyelination and dedifferentiation-proliferation functions associated with nerve cell injury [22]. In small diameter, nonmyelinated axons reprograming of surrounding

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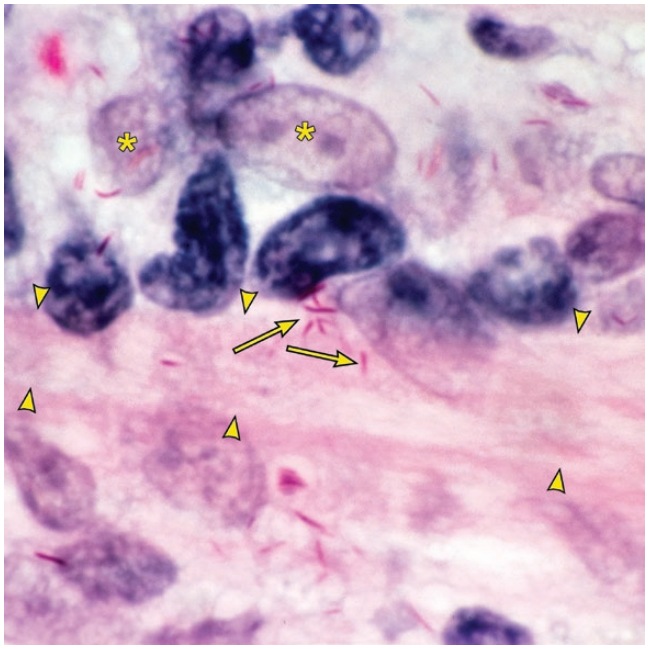

Figure 1. Histopathology of dermal nerve twig involvement with *Mycobacterium leprae*. Fite-Faraco (original magnification, ×1000) acid-fast stain of skin biopsy from lesion of Case 2 shown in Figure 3. Arrowheads mark the borders of a cutaneous nerve twig. Arrows point to acid-fast bacilli partitioning 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.

Schwann cells to a dedifferentiated phenotype may interfere with nerve conduction through as yet unknown mechanisms [23]. 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 [24]. 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 [16].

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 nonendemic 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. In this article, we present teaching cases that 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.

Patient Consent Statement

Consent to photograph and publish the photos was obtained from all 5 patients. The article type ("ID Teaching Cases") did not require formal approval by Ethics Committees. Likewise formal participant consent forms were not required.

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

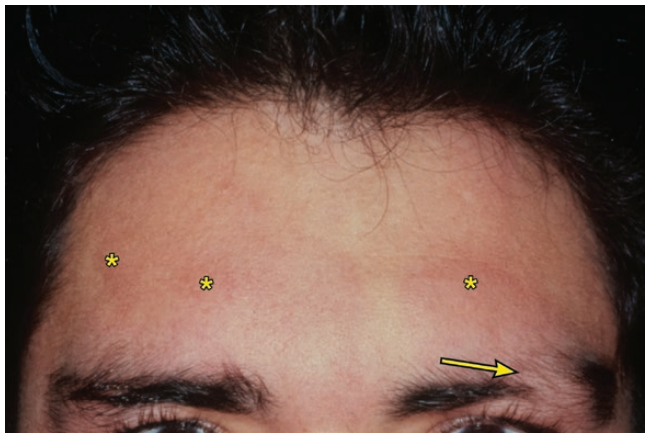

Figure 2. Focal area of eyebrow alopecia due to impaired new hair growth. Arrow points to focal area of left eyebrow hair loss. Asterisks mark subtle erythematous slightly raised lesions on the forehead. One of these on the left forehead extends into the area of the eyebrow (not well captured in the photo), where partial hair loss is evident. This can progress to complete loss of eyebrow and eyelid hair, a condition known as madarosis.

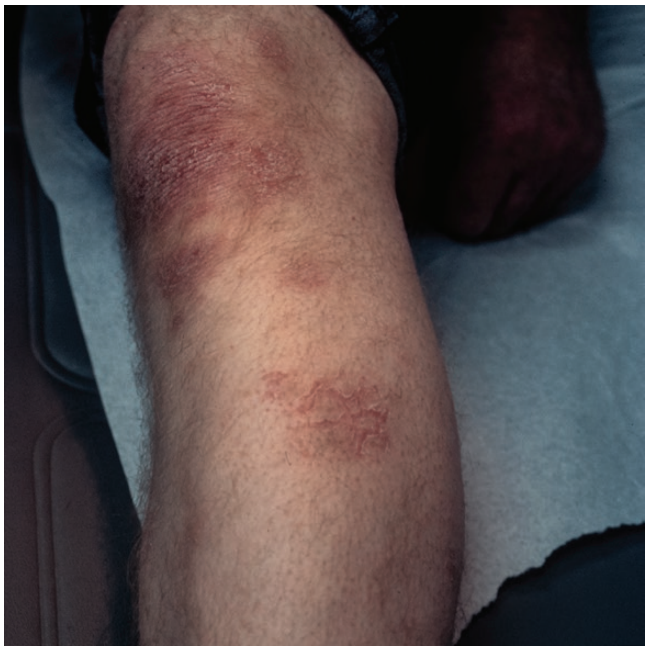

Figure 3. Xerodermatous lesions resulting from denervation of pilosebaceous units. Scaling, dry hairless lesions on the anterior left leg. Photograph of the patient was taken during winter season in cold, arid climate conditions. Biopsy from one of the lesions is shown in Figure 1.

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 1 year for paucibacillary disease. Complete remission was obtained. Two years after completing treatment, he developed skin lesions that 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 that were dry, scaling, and hairless (Figure 3). [The photograph was taken during the arid winter season in the Rocky Mountains.] Skin biopsy was performed that 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 except for the palms and soles. Complex lipid secretions help smooth, lubricate, and maintain hydration of the skin [28]. 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. Antileprosy 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 [29]. 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 [30]. Apocrine sweat glands, possibly vestigial in humans, are confined primarily to the axillae and

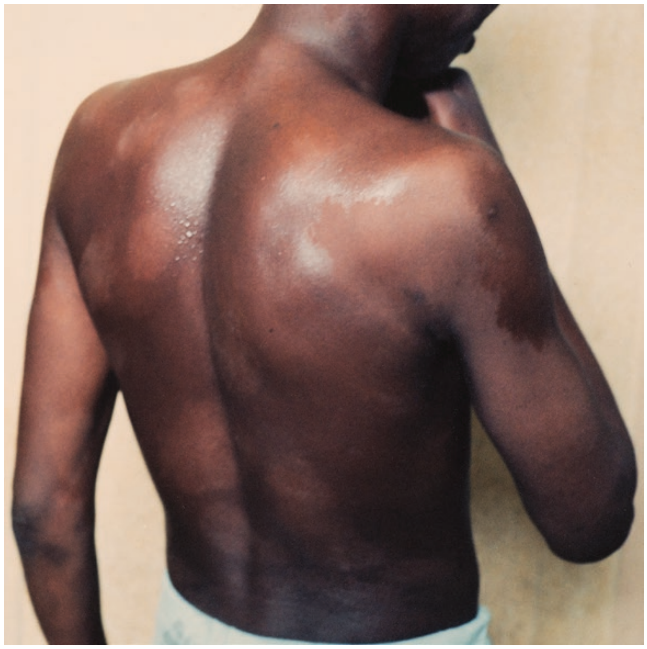

Figure 4. Eccrine sweat gland involvement. Anhidrosis is evident especially over right scapular and triceps areas. Uninvolved skin shows beads of sweat. The photograph was taken in a tropical climate at ambient temperature approximately 34°C. Note hypopigmentation of anhidrotic skin.

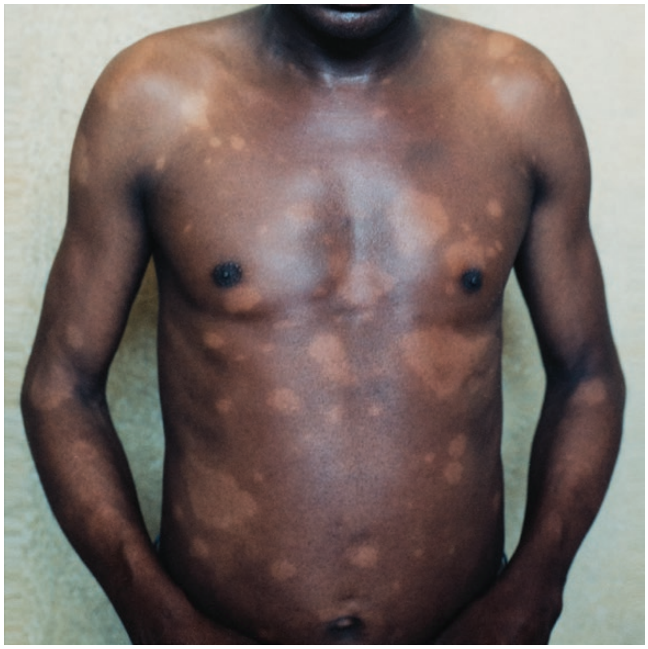

Figure 5. Hypopigmentation in areas of cutaneous nerve involvement. Large and small areas of geographical macular hypomelanization are seen on the trunk. The lesions can be distinguished from tinea versicolor by testing for anesthesia to light touch and temperature/pain sensation. Loss of neuropeptide secretions from locally involved cutaneous nerves may explain the inhibition of melanization in affected areas of skin.

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 [31].

Case 4

The patient was referred to Dermatology Clinic at Muhimbili National Hospital in Dar es Salaam, Tanzania. His home was in western Tanzania near Lake Tanganyika. He complained of patches of light-colored skin, which were treated topically with antifungal 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 [32]. Mechanisms affecting melanization can be traced to secretion of neuropeptides from peripheral nerve endings [33]. The melanocortins, eg, melanocyte stimulating hormone, and the beta-endorphins are implicated in controlling skin pigmentation by modulating melanin synthesis in epidermal melanocytes [34, 35]. 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 [36, 37]. 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 that were managed with prednisone. No further information was available.

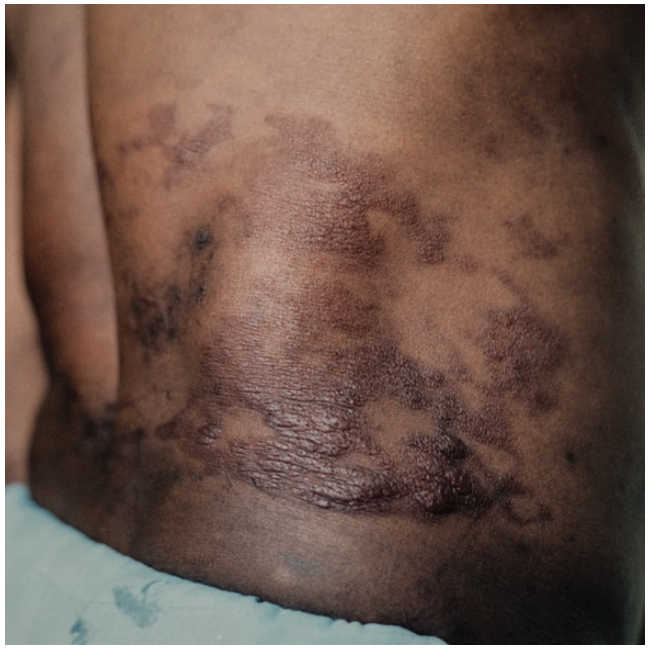

Figure 6. Hyperpigmented flank lesions in a woman with multibacillary leprosy. Hyperpigmented, indurated plaques are seen on the right flank. Increased melanization may occur as a result of drug treatment or intralesional induction of melanin synthesis by inflammatory mediators that stimulate proopiomelanocortin-derived peptides (see text for explanation).

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 [38]. Interleukins and lipid mediators of inflammation (prostaglandins and leukotrienes) promote pigmentation in areas of the skin perturbed by injurious stimuli [39]. These systemic and local responses may contribute to the hyperpigmentation of HD skin lesions like those shown in Figure 6.

CONCLUSIONS

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 use largely cholinergic neurotransmission. These autonomic efferents govern physiological functions of the skin appendages. *Mycobacterium leprae* infection inhibits autonomic nerve transmission by parasitism of Schwann cells that surround autonomic nonmyelinated 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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References

1. Lockwood DN, Saunderson PR. Nerve damage in leprosy: a continuing challenge to scientists, clinicians and service providers. Int Health **2012**; 4:77–85.
2. van Brakel WH, Nicholls PG, Wilder-Smith EP, et al.; INFIR Study Group. Early diagnosis of neuropathy in leprosy–comparing diagnostic tests in a large prospective study (the INFIR cohort study). PLoS Negl Trop Dis **2008**; 2:e212.
3. Bhat RM, Prakash C. Leprosy: an overview of pathophysiology. Interdiscip Perspect Infect Dis **2012**; 2012:181089.
4. Ng V, Zanazzi G, Timpl R, et al. Role of the cell wall phenolic glycolipid-1 in the peripheral nerve predilection of *Mycobacterium leprae*. Cell **2000**; 103:511–24.
5. Tapinos N, Ohnishi M, Rambukkana A. ErbB2 receptor tyrosine kinase signaling mediates early demyelination induced by leprosy bacilli. Nat Med **2006**; 12:961–6.
6. Wilder-Smith EP, Van Brakel WH. Nerve damage in leprosy and its management. Nat Clin Pract Neurol **2008**; 4:656–63.
7. Tapinos N, Rambukkana A. Insights into regulation of human Schwann cell proliferation by Erk1/2 via a MEK-independent and p56Lck-dependent pathway from leprosy bacilli. Proc Natl Acad Sci U S A **2005**; 102:9188–93.
8. Fonseca AB, Simon MD, Cazzaniga RA, et al. The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy. Infect Dis Poverty **2017**; 6:5.
9. Serrano-Coll H, Salazar-Peláez L, Acevedo-Saenz L, Cardona-Castro N. *Mycobacterium leprae*-induced nerve damage: direct and indirect mechanisms. Pathog Dis **2018**; 76.
10. Spierings E, de Boer T, Wieles B, et al. *Mycobacterium leprae*-specific, HLA class II-restricted killing of human Schwann cells by CD4+ Th1 cells: a novel immunopathogenic mechanism of nerve damage in leprosy. J Immunol **2001**; 166:5883–8.
11. Nath I, Saini C, Valluri VL. Immunology of leprosy and diagnostic challenges. Clin Dermatol **2015**; 33:90–8.
12. Wisniewski HM, Bloom BR. Primary demyelination as a nonspecific consequence of a cell-mediated immune reaction. J Exp Med **1975**; 141:346–59.
13. Yamamura M, Wang XH, Ohmen JD, et al. Cytokine patterns of immunologically mediated tissue damage. J Immunol **1992**; 149:1470–5.
14. Aarão TLS, de Sousa JR, Falcão ASC, et al. Nerve growth factor and pathogenesis of leprosy: review and update. Front Immunol **2018**; 9:939.
15. Oliveira RB, Ochoa MT, Sieling PA, et al. Expression of Toll-like receptor 2 on human Schwann cells: a mechanism of nerve damage in leprosy. Infect Immun **2003**; 71:1427–33.
16. Hess S, Rambukkana A. Cell biology of intracellular adaptation of *Mycobacterium leprae* in the peripheral nervous system. Microbiol Spectr **2019**; 7.
17. Hunter SW, Brennan PJ. A novel phenolic glycolipid from *Mycobacterium leprae* possibly involved in immunogenicity and pathogenicity. J Bacteriol **1981**; 147:728–35.
18. Hunter SW, Fujiwara T, Brennan PJ. Structure and antigenicity of the major specific glycolipid antigen of *Mycobacterium leprae*. J Biol Chem **1982**; 257:15072–8.
19. Rambukkana A. How does *Mycobacterium leprae* target the peripheral nervous system? Trends Microbiol **2000**; 8:23–8.
20. Rambukkana A, Salzer JL, Yurchenco PD, Tuomanen EI. Neural targeting of *Mycobacterium leprae* mediated by the G domain of the laminin-alpha2 chain. Cell **1997**; 88:811–21.
21. Rambukkana A, Yamada H, Zanazzi G, et al. Role of alpha-dystroglycan as a Schwann cell receptor for *Mycobacterium leprae*. Science **1998**; 282:2076–9.
22. Rambukkana A. Usage of signaling in neurodegeneration and regeneration of peripheral nerves by leprosy bacteria. Prog Neurobiol **2010**; 91:102–7.
23. Hess S, Rambukkana A. Bacterial-induced cell reprogramming to stem cell-like cells: new premise in host-pathogen interactions. Curr Opin Microbiol **2015**; 23:179–88.
24. Rambukkana A, Zanazzi G, Tapinos N, Salzer JL. Contact-dependent demyelination by *Mycobacterium leprae* in the absence of immune cells. Science **2002**; 296:927–31.
25. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: basic mechanisms and clinical applications. Clin Auton Res **2003**; 13:256–70.
26. Heitman N, Sennett R, Mok KW, et al. Dermal sheath contraction powers stem cell niche relocation during hair cycle regression. Science **2020**; 367:161–6.
27. Zhang B, Ma S, Rachmin I, et al. Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. Nature **2020**; 577:676–81.
28. Fluhr JW, Mao-Qiang M, Brown BE, et al. Glycerol regulates stratum corneum hydration in sebaceous gland deficient (asebia) mice. J Invest Dermatol **2003**; 120:728–37.

29. Rao MS, Landis SC. Cell interactions that determine sympathetic neuron transmitter phenotype and the neurokines that mediate them. J Neurobiol **1993**; 24:215–32.
30. Sato K, Dobson RL. Regional and individual variations in the function of the human eccrine sweat gland. J Invest Dermatol **1970**; 54:443–9.
31. Shappell SB, Keeney DS, Zhang J, et al. 15-Lipoxygenase-2 expression in benign and neoplastic sebaceous glands and other cutaneous adnexa. J Invest Dermatol **2001**; 117:36–43.
32. Roosterman D, Goerge T, Schneider SW, et al. Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. Physiol Rev **2006**; 86:1309–79.
33. Peters EM, Ericson ME, Hosoi J, et al. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. J Invest Dermatol **2006**; 126:1937–47.
34. Hiramoto K, Kobayashi H, Ishii M, et al. Increased alpha-melanocyte-stimulating hormone (alpha-MSH) levels and melanocortin receptors expression associated with pigmentation in an NC/Nga mouse model of atopic dermatitis. Exp Dermatol **2010**; 19:132–6.
35. Kauser S, Schallreuter KU, Thody AJ, et al. Regulation of human epidermal melanocyte biology by beta-endorphin. J Invest Dermatol **2003**; 120:1073–80.
36. Byers HR, Maheshwary S, Amodeo DM, Dykstra SG. Role of cytoplasmic dynein in perinuclear aggregation of phagocytosed melanosomes and supranuclear melanin cap formation in human keratinocytes. J Invest Dermatol **2003**; 121:813–20.
37. Van Den Bossche K, Naeyaert JM, Lambert J. The quest for the mechanism of melanin transfer. Traffic **2006**; 7:769–78.
38. Schauer E, Trautinger F, Köck A, et al. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. J Clin Invest **1994**; 93:2258–62.
39. Wintzen M, Yaar M, Burbach JP, Gilchrest BA. Proopiomelanocortin gene product regulation in keratinocytes. J Invest Dermatol **1996**; 106:673–8.