

## Special Article

# Revisiting Hansen's Disease: Recognizing the Many Neurodermatologic Faces and its Diagnostic Challenges

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## Abstract

Hansen's disease (HD) looms still as a public health problem. Conventional wisdom and teaching largely view HD as a predominantly dermatologic disorder with much emphasis in the dermatology postgraduate curriculum. This review attempts to reorient this view and reemphasize that HD has primarily neurologic underpinnings since *Mycobacterium leprae* is an intracellular neurotropic bacterium. The main thrust of this article would, therefore, be a neurologist's perspective of HD. The cutaneous manifestations of HD are the sequelae of the neurobiology of *M. leprae*, its selective predilection to human Schwann cells, neurovascular bundle and its localization in the intracutaneous nerve plexus of the skin. We discuss the nuances of HD as a "great imitator," the many faces of its neurodermatologic clinical presentation, the neurologic basis of HD clinical examination, and its diagnostic and therapeutic challenges.

**Keywords:** Armadillo model, chameleons, Hansen's disease, high-resolution ultrasonography, leprosy reactions, leprosy, mimics, neurobiology, pure neuritic leprosy, Schwann cells, small fiber neuropathy, temperature-linked pattern

## INTRODUCTION

Leprosy is one of the world's oldest and most dreaded diseases that have tormented humans throughout history, leaving lasting impressions on religion, literature, and art.<sup>[1]</sup> The first historic mention of leprosy in India dates back to as early as 600 BC, where it is denoted by a Sanskrit term "Kushtha," literally meaning "eating away."<sup>2</sup> Reports of the presence of leprosy can also be found in the ancient writings from Japan (10<sup>th</sup> century BC) and Egypt (16<sup>th</sup> century BC). In 1873, Gerhard-Henrik Armauer Hansen, a Norwegian scientist, first identified the bacteria in the year 1873, making it the first germ to be identified as a causative microorganism for any disease. Leprosy being documented, stigmatized, and feared from antiquity to modernity, is still endemic in many parts of the world, in the "elimination era" with a lot of questions, challenges, and controversies yet to be answered. Leprosy (or Hansen's disease [HD]) remains an important public health challenge globally, with an estimated 5.5 million total number of cases and 200,000–300,000 new cases reported annually.

The cardinal manifestations of HD are the combination of the well known characteristic dermatologic features in addition to the various neurological presentations (a neuro-dermatologic disease).

The presentation of HD could, however, be pleomorphic and heterogeneous with phenotypic chameleons and masqueraders, increases the diagnostic dilemma, and broadening the differential diagnosis. Clinical manifestations can range from a single skin lesion to a generalized infiltration or from a mononeuritis to a symmetric polyneuropathy. Recognizing the disease in its early or late phase is challenged by a number of simulating dermatoses and neuropathies. The varied, atypical, and unusual clinical presentations of HD underscores the need for interdisciplinary awareness not only between the neurologist and dermatologist but also include the ophthalmologist, rheumatologist, otolaryngologist, and the dentist. Furthermore, apart from the regular manifestations, leprosy sometimes exhibits the reaction status (lepra reactions) that can further impose diagnostic and therapeutic challenges.

The challenges that could involve both the dermatologist and the neurologist occur when the typical dermatologic features

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are absent such as typical cutaneous lesions (erythematous, macules, and nodules/lepromas – face, earlobe, forearm, and arm), resorption of toes, trophic ulcers, and madarosis. In such cases, there is an urgent need to consider pure neuritic leprosy (PNL) in the differential diagnosis of neuropathies in general. HD is a disease that is eminently treatable and PNL does underscore the importance of meticulous neurologic examination. It is absolutely necessary for the treating physician to understand the various neurological presentation and nondermatological presentations of this disease, to make an exact diagnosis clinically or by resorting to the need for various diagnostic tests since HD is treatable disease with preventable morbidity and disability. Leprosy can present in many diverse ways which can be confused with many treatable and nontreatable, infectious and noninfectious forms. The various face of HD presentation, its chameleons (*What are some unusual and atypical clinical phenotypes of leprosy?*) and masqueraders/mimics (*What presentation may simulate leprosy?*), are of paramount importance for “pattern recognition” and will be the main impetus of this review.

## THE NEUROLOGICAL PERSPECTIVE

Nerve damage is the hallmark of leprosy.<sup>[2]</sup> Although *Mycobacterium leprae* has been recognized as the causative agent of leprosy for more than a century, the underlying pathophysiology of neuropathic damage several important knowledge gaps does exist in our understanding the molecular and genetic mechanisms of HD. Despite widespread implementation of effective multidrug therapy (MDT), leprosy has not been eliminated. Leprosy continues to be a challenge to health worldwide. Ninety-one countries in the world are endemic for leprosy; India (Nepal), Brazil, Myanmar/Burma, Africa (Angola, Central African Republic, Congo, Madagascar, Mozambique, and Tanzania), and Indonesia are the leading countries with maximum cases. India reports over 50% of the world’s leprosy cases.<sup>[3,4]</sup> The review, therefore, starts with knowledge gaps in our understanding of the neurobiology and dwells on the complex multitude of agent–host interactions. This would set the way forward to find solutions to unsolved matters in leprosy research, development of novel drug target, leprosy vaccine, and an array of immunodiagnostics from the bench to the bedside.

Since *M. leprae*, an intracellular obligate bacterium that exhibits selective peripheral nerve neurotropism, it is pertinent to dwell on the neurobiological, host-inflammatory, and complex interplay of bacterial-mediated molecular aspects. This will explicate and pave the way forward in the “therapeutic pipeline” to exploit potential development of novel drugs targets, molecular targets, and immunodiagnostics in leprosy research. The next sections of this review will allude to the neurobiological underpinnings of the neurological symptoms of HD, the importance of meticulous-focused neurological examination, to reappraise the “typical” features of lepromatous neuropathy, and finally, to recognizing the many faces and diagnostic challenges of lepromatous neuropathy.

## THE NINE-BANDED ARMADILLO MODEL FOR LEPROSY RESEARCH

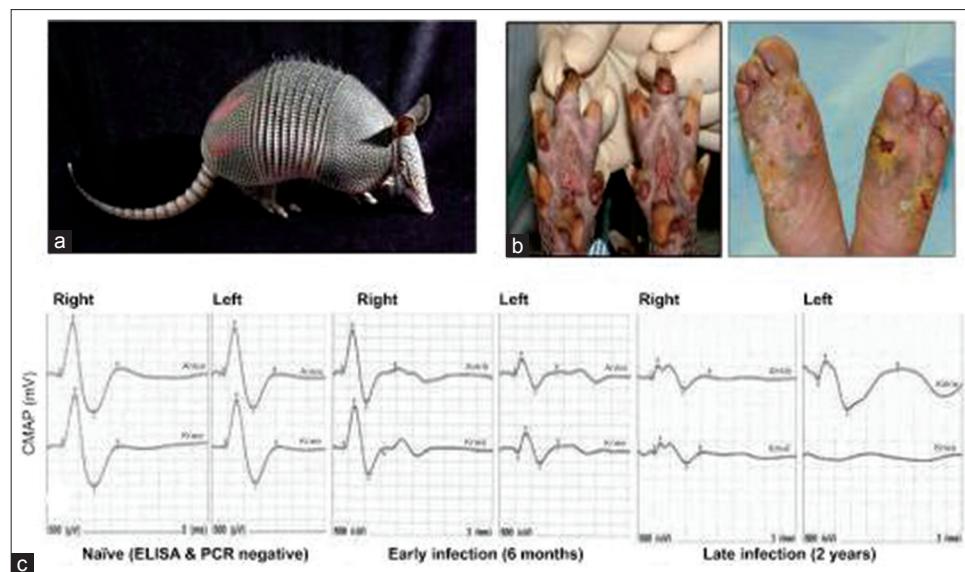
The specific neurobiologic underpinnings to explicate the selective neurotropism, i.e., *M. leprae*-host cell interaction is certainly intriguing. *M. leprae* has never been cultivated in artificial bacteriological media (*in vitro*). In view of this, the intricate mechanisms by which this bacterium induces nerve injury remain largely unknown. However, using another natural nonhuman vertebrate host for *M. leprae*, the nine-banded armadillos (*Dasypus novemcinctus*) as models of leprosy pathogenesis and nerve damage, the knowledge gaps can be narrowed. The nine-banded armadillo remains as the only immunologically intact species which regularly develops lepromatous leprosy. Thus, *M. leprae* infection of the armadillo closely recapitulates features of human leprosy and is the best available model of early nerve injury in this disease. Figure 1 depicts the similar lepromatous leprosy changes in the armadillo and a human leprosy patient with the corroborating noninvasive electrophysiological aberrations, in terms of progressive nerve conduction deficit in compound motor action potential that occur in lepromatous nerve damage.<sup>[5]</sup>

The advances using armadillo-leprosy model for advanced molecular studies will be pivotal in providing new insights into the oldest known infectious neurodegenerative disorder, in addition to piloting new therapies and diagnostic regimens in the future. The armadillo model will throw light on bacterial susceptibility and propagation mechanisms, armadillo gene expression and disease susceptibility and leprosy resistance, armadillo-specific molecular and immunological markers, nerve morphometric, histologic, immunohistochemistry and electrophysiologic features to study the inflammatory and demyelination cascade of events, as well as the development of early diagnostics, therapeutics, and leprosy vaccines. The use of armadillos in leprosy research will continue to “fill our glass half empty” neurobiologic underpinnings of this disease.<sup>[5,6]</sup> A recent research did propound the zebrafish as yet another experimental animal model for understanding the pathogenesis of *M. leprae* granulomatous infection.<sup>[7]</sup>

## *MYCOBACTERIUM LEPRAE* – HOST-HUMAN SCHWANN CELL NEUROTROPISM

### The neurobiology of nerve injury

Nerve injury is a central feature of the pathogenesis of leprosy, and this section attempts to review the plausible factors; current research data; and new insights into the *M. leprae* epitopes-host cell interaction at a Schwann cell (SC)/macrophage and receptor level; the role of dendritic cells, SC-mitochondrial bioenergetics, and genetic, immunological, and inflammatory neuromediators; and the role of epineurium and endoneurium endothelial cells of the neurovascular bundle in the pathogenesis and pathophysiology of lepromatous neuritis.<sup>[8,9]</sup> The host cell factors and molecular in the mediation of nerve injury are summarized in Table 1.



**Figure 1:** The armadillo is the only natural host of Hansen's disease, aside from humans. (a) Nine-banded armadillo. (b) Armadillo in the late stages of Hansen's disease with lesions on its feet (left) and a human leprosy patient (right). (c) Representative waveforms illustrating progressive nerve conduction deficit in (compound motor action potential; mV; y-axis) leading to complete conduction block in late infection. The upper lines show responses to stimulation at the ankle and the lower ones to the knee<sup>[5]</sup>

By hijacking the human SC of the rich plexus of nerves in the superficial dermis, intradermal and intracutaneous nerves, *M. leprae* subverts SC Krebs's cycle and pentose phosphate pathway metabolism.<sup>[10]</sup> *M. leprae* alters the SC mitochondrial metabolism of glucose, facilitates glutathione regeneration, controls free radical production, and overrides the host cell free-radical defenses thus increasing its viability and growth. The complex modulation of SC and axons results in axonal lower Krebs cycle activity and a subsequent mitochondrial loss of function and swelling, leading to lower axonal energy production, global axonal metabolism reduction, neurofilament hypophosphorylation, demyelination, and axonal loss leading to loss of neural functions.<sup>[11]</sup> Another recent insight into the SC neurotropism revealed *M. leprae* causes neural injury and axonal death by downregulating SC differentiation and myelination genes such as MBP, MPZ/P0, and Krox 20.<sup>[12]</sup> It is intriguing to take cognizance that this novel intracellular bacteria adopts metabolic remodeling between the host and itself, and apart from glucose metabolism alterations, macrophages infected with *M. leprae* does affect the lipid metabolism too.<sup>[13]</sup> *M. leprae* imports lipids from foamy macrophages and is dependent on fatty acids for growth, energy, and survival in infected macrophage (lipid droplet formation and foamy host cells) and is of the most unique determinant for *M. leprae* persistence and virulence.

Recent evidence from infected armadillos suggests epineurial and endoneurial endothelial cells of the peripheral nerve vasculature to be the gatekeepers, by which *M. leprae* infects nerves.<sup>[14]</sup> The pathogenesis of neuropathy in leprosy then undergoes an intricate and complex dynamic sequence of *M. leprae*-SC adhesion, immunologic, and inflammatory processes involving peripheral nerve endothelial cells [Figure 2].<sup>[15]</sup>

**Table 1: A summary of host cell factors in the *Mycobacterium leprae*-Schwann cell interaction producing lepromatous nerve injury**

#### Host cell factors

Schwann cells and receptors

Schwann cell-axon unit

Transaxonal spread

Unmyelinated axon damage of dermal/intradermal/superficial cutaneous nerves in cooler regions with 33°C–36°C

Reprogramming and downregulation of Schwann cells to stem cell-like cells

Neurovascular bundle-epi/perineurial blood vessels endothelium

Macrophage activation-toll-like receptors-VDR-Vitamin D-dependent antimicrobial pathway

#### Dendritic cells

Proinflammatory cytokines-triggers apoptosis

Downregulation of neurotrophic factors

Host genetic factors – upregulation of genes for pro-inflammatory cytokines

Genomewide association study of leprosy susceptibility genes

Gene susceptibility-SNPs

VDR: Vitamin D receptor, SNP: Single nucleotide polymorphism

Since the SCs synthesize myelin, demyelinating and axonal nerve injury ensues when they become infected with *M. leprae*. The potential mechanisms of binding of *M. leprae* to the SC may be attributed to the binding of the phenolic glycolipid I (PGL-I) and/or Hlp (histone-like protein) present on the surface of the bacteria specifically binding to alpha-dystroglycan (alpha-DG) present on the SC surface in the presence of the G domain of the alpha 2 chain of laminin-2 complex in the basal lamina of SC-axon units. After *M. leprae* adhere to the SC surface of dermal

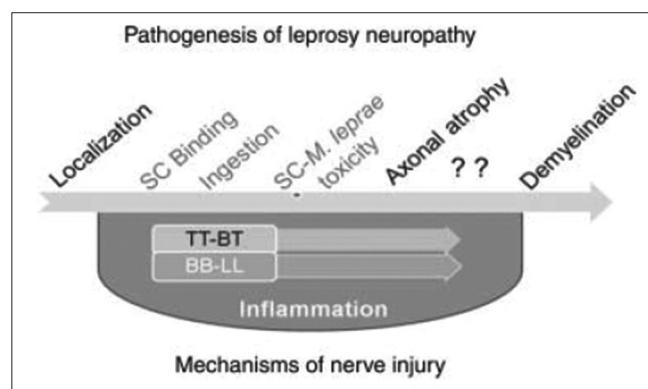
axons, they are slowly phagocytized and spread from one SC the next and/or by transaxonal transport. Through the various genetic and energy metabolism modulation of the SCs, SC loss and SC apoptosis, and induction of cytotoxic T-cells evoking concurrent immunological/inflammatory (pro-inflammatory cytokines) events by the ingested *M. leprae*, a conducive environment suitable for preservation and proliferation of *M. leprae* and consequent neural injury is established.<sup>[15]</sup>

Another facet of *M. leprae*-induced nerve injury involves dermal nerve neurotrophins such as nerve growth factor, brain-derived neurotrophic factor, and NT3. Neurotrophins are growth factors with crucial roles in neural pathophysiology. These mediators functionally modulate nociceptive fibers and changes in neurotrophins expression have been correlated with early loss of nociception in leprosy. Our current research data does indicate alterations in neurotrophins, along with inflammatory process (through pro-inflammatory cytokines such as tumor necrosis factor [TNF]- $\alpha$  and transforming growth factor  $\beta$ ) and the induction human SC apoptosis to be involved in the establishment of peripheral nerve damage.<sup>[16,17]</sup>

Investigating the various complex pathways and pathomechanistic mediators in neural injury, demyelination, and axonal loss would be an important arena that could potentially be exploited in leprosy research for developing novel drugs, vaccines, and immunodiagnosis for leprosy.

## NEUROLOGIC BASIS FOR A “FOCUSED” LEPROSY CLINICAL EXAMINATION

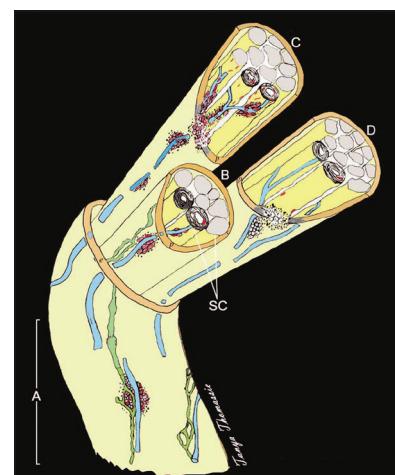
*M. leprae* being a neurotropic obligate intracellular bacterium with predilection to spread from the superficial dermal neurovascular bundle and of circulation, adhere to the endothelial cells of the endoneurium and perineurium, hijack the SC, and spread in a transaxonal route to the rich plexus of superficial dermal, intradermal, and intracutaneous nerves of the skin [Figures 3 and 4].



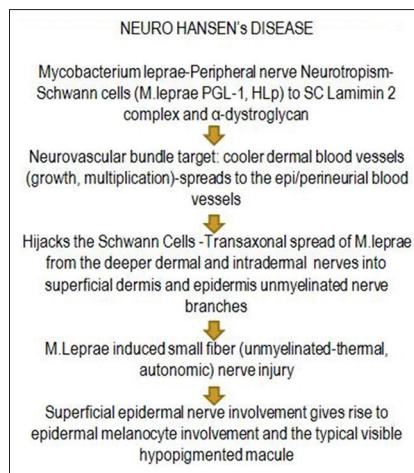
**Figure 2:** A working draft depicting the “steps” in the pathogenesis of nerve injury in leprosy: Localization of *Mycobacterium leprae* to nerve, Schwann cell infection and responses, axonal atrophy, and finally demyelination<sup>[15]</sup>

There are two peculiarities in the selective localization and involvement of nerves in lepromatous nerve involvement. First, leprosy is a localized infective neuropathy since it selectively affects the rich plexus of nerves in the superficial dermis. The plausible reason for this localized cutaneous nerve involvement is that a lower temperature (28–32°C) is conducive for the multiplication of *M. leprae* in the superficial dermis, intracutaneous nerve branches, erector pili muscles, and epidermal melanocytes. From a neurologist’s clinical perspective, leprosy neuropathy has a characteristic and preferential “temperature-linked pattern” of localized cutaneous sensory loss, and this unique pattern could differentiate the classical generalized “glove and stocking” sensory loss in “dying-back” neuropathies. The second cardinal feature is the “small fiber neuropathy” involvement in leprosy affecting the unmyelinated and thinly myelinated Type C and thinly myelinated A $\delta$  fibers. These fibers subserve autonomic function, cutaneous sensory modalities of temperature (warm > cold), and pain.

It is crucial to recognize that the nerve damage by the lepra bacilli becomes clinically manifest only when 25%–30% of the nerve fibers in a nerve trunk become nonfunctional. Below this threshold of nerve fiber dysfunction, the routine clinical neurologic examination would fail to show any cutaneous sensory deficits, and this phenomenon has been described as “quiet nerve paralysis,” and/or “silent neuropathy.”



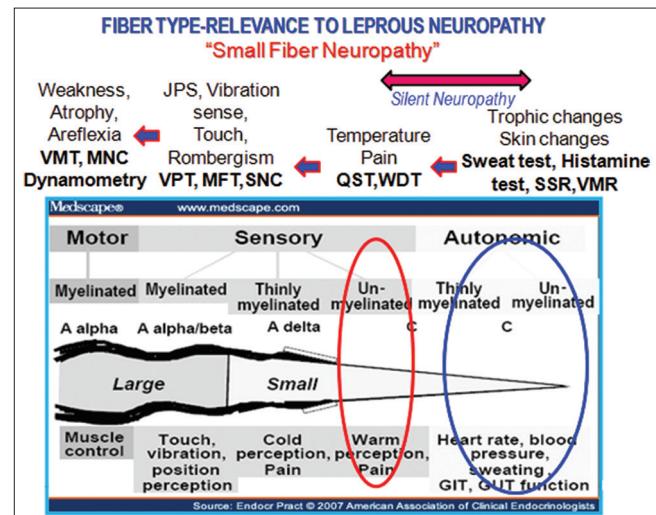
**Figure 3:** A proposed pathogenesis model of infection of peripheral nerve by *Mycobacterium leprae* through blood vessels. A cutaneous nerve with three fascicles is shown. [A] (a) Initially, colonization of the epineurium (e) occurs when bacilli (red) localize in cells in and around blood vessels (blue). [B] Entry of *Mycobacterium leprae* into the endoneurial compartment proceeds along blood vessels from foci on and within the perineurium (p), extending through it into the interior of the nerve. [C] In poor immune host response (lepromatous leprosy), the bacilli proliferate within macrophages and Schwann cells causing perineurial inflammation and thickening (proliferation) and an increasing bacterial load both in the epineurium and in the endoneurium. [E] In cases of an effective host cellular immunity (tuberculoid leprosy), a granulomatous response follows at sites of infection near epineurial and endoneurial vessels and Schwann cells<sup>[14]</sup>



**Figure 4:** Schematic diagrammatic representation of the neuropathogenetic steps in neurotropism and localization of *Mycobacterium leprae* to involve the peripheral nerve and skin

(SN). “Clinically manifest disease” once it is apparent on clinical examination, it unfortunately signals that the leprosy nerve damage is already quite advanced. Nevertheless, SN (subclinical leprosy neuropathy) could be detected at the earliest by specific nerve function assessment (NFA) before the occurrence of clinical nerve damage event. The subclinical nerve fiber impairment (NFI) relies on NFA beyond the standard clinical tests such as the Semmes–Weinstein monofilament test (MFT), Grip dynamometry, and Voluntary muscle testing. Vibrometry (vibration perception threshold [VPT]) did not appear to have much additional advantage over the standard established methods of sensory testing. The INFIR cohort study did throw light on the sensitivity of various NFA diagnostic tests in improving the early detection subclinical neuropathy using instruments that assess thick myelinated, thin myelinated, as well as unmyelinated fiber systems.<sup>[18]</sup> As shown in Figure 5, the small fiber nerve dysfunction in a “temperature-linked pattern” was detected the earliest sensory nerve conduction (SNC) measurements (SNAP amplitude) and quantitative sensory testing (QST). QST involved thermal threshold, namely, testing the warm and cold detection thresholds.

In early and silent leprosy neuropathy that preferentially involves the small fibers, the preferential NFI would be the Type C-mediated autonomic dysfunction (histamine test, sweat test, vasomotor test-digital laser Doppler velocimetry, and sympathetic skin response), followed by impairment of Type C/A $\delta$  fibers reflected by temperature perception test deficits in warm perception, pain perception, and finally cold perception [Figure 5]. Only in advanced leprosy neuropathy is the “large nerve fiber” type (A $\alpha$ /A $\beta$ ) involved to give rise to muscle wasting (correlating with INFIR-NFA-motor nerve conduction – MNC abnormalities) and impairment in proprioceptive sensory modalities (abnormalities in vibration perception, joint position sense, and deep tendon reflex, clinically; correlating with INFIR NFI-VPT) and MFT abnormalities. This knowledge forms the fundamental bedside clinical algorithm to



**Figure 5:** A diagram depicting the Erlanger and Grasser's classification of fibers types and its function in a peripheral nerve. According to the size and speed of conduction, the nerve fibers are classified into three different categories, namely, A, B, and C. Symptoms and signs of peripheral neuropathy ascribed to the type of fiber loss in neuropathies. (Source: Medscape, Endocrine Practice 2007)

have a focused and targeted neurologic examination in detecting the neurodermatologic manifestation of typical HD.

## NEUROLOGIC EXAMINATION FINDINGS IN LEPROSY NEUROPATHY

The neurological examination in clinical leprosy is dictated by the two specific features of involvement, i.e., preferential “temperature-linked pattern” of localized cutaneous sensory loss due to early “small fiber neuropathy” impairment in nerve functions on bedside clinical examination.<sup>[19]</sup>

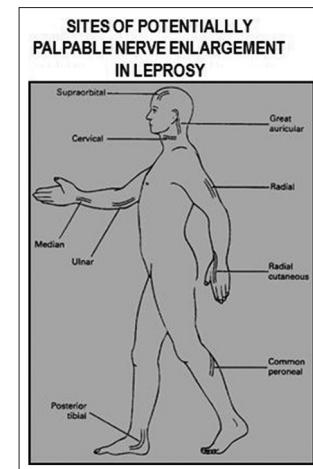
### Temperature-linked pattern: Predilection of superficial dermal and intracutaneous nerves

Since *M. leprae* reproduces at temperatures of 28°C–32°C, a unique pattern of neurodermatologic features appears. The host immune response determines the selective destruction of epidermal melanocytes by cytotoxic lymphocytes, aberration in the melanocytic tyrosinase enzyme, and a disturbed transfer of melanosomes from melanocytes to keratinocytes by *M. leprae* that leads to the typical presence of hypopigmented macula-anesthetic skin patches (lepromatos leprosy) or absence (as in PNL).<sup>[20,21]</sup> The hypomelanotic, anesthetic patch(s) with feathered borders and thickened regional nerve are virtually diagnostic of the disease. The temperature-linked deficits (temperature-linked sensory nerve fiber deficits) result from destruction of intracutaneous nerve network and the involvement of larger nerves in cooler locations. Deep modalities mediated by peripheral nerves such as muscle stretch reflexes, vibration and position sense, and most motor functions (A $\alpha$ , A $\beta$  fibers) tend to be unaffected because these nerves are embedded deep in tissues, which keeps them warm. Motor deficits are most often in the distribution of nerves

close to the body surface and in coolest regions of the body. The nerves so affected may be thickened, hardened, and at times even visible. Cranial nerves are affected only where they become superficial and cool, resulting in patchy loss of functions in patterns specific for leprosy. Autonomic and vasomotor skin deficits such as anhidrosis, dryness and fissuring of hands and feet, ichthyosiform changes of the arms and legs, hair loss, trophic, and mutilating acrodystrophic changes also occur in superficial cool areas of the body, whereas the autonomic fibers that lie more deeply within the body are not involved and hence postural hypotension, bladder dysfunction, nocturnal diarrhea, and erectile dysfunction as seen in other hereditary autonomic and small fibers neuropathies.

The cardinal symptom of leprosy is sensory loss, that is, patchy, scattered, asymmetrical pattern, not truly distal. The sensory deficits pattern (temperature-linked sensory loss with islands of preserved sensation) has a predilection to involve the earlobe and helices, pinnae of ears, corneal sensations, the nose and malar area of the face, medial and dorsal aspects of the forearm and hands, the elbow region, anterior knee regions, breast, central abdomen, the buttocks, anterolateral aspects of the legs, and the dorsal aspects of the foot. This unique pattern of sensory involvement does not conform to the "glove-stockings" sensory loss seen in other hereditary, metabolic, and toxic neuropathies. The intracutaneous sensory deficits at the borderline areas of the forehead and the abrupt return to normal sensations at the hairline ("hair-line" sign) elegantly depicts the relevance of the temperature-linked sensory deficits since there will be an increase of 1.5°C–3°C in temperature under the scalp hair. It is also noteworthy that certain regions of the body show consistent sparing because of the greater warmth of regions such as the palms and soles, the axillae, the sterna area, a stripe of variable width up to the center of the back from the intergluteal fold to the neck, inguinal creases, and the popliteal fossa. The intracutaneous temperature linked sensory deficits are usually accompanied with the "neighborhood signs" of palpable, beaded, tender, and irregular thickening of the superficial subcutaneous nerves [Figure 6].

The pattern of facial sensory impairments is also characteristic by way of the patchy nonuniform involvement of facial and trigeminal nerve superficial intracutaneous branches. The superficial branches of the seventh cranial nerve involved either unilaterally or bilaterally involve the orbicularis oculi, the forehead, branches over zygomatic arch, orbital rim, and the mandible (pes anserinus). It is unique to note the differential involvement of facial nerve branches in that the medial segments of the frontalis muscle are paralyzed before the lateral. In this case, when such a patient attempts eyebrow elevation, only the lateral aspects rise, resulting in a characteristic V configuration giving rise to the description of "devilish appearance." Involvement of the small nerve branches to the orbicularis oris muscle does produce localized outpouching of the lips at the corners of the mouth. The differential and preferential involvement of the superficial muscles forming the



**Figure 6:** A summary showing the functional nerve fiber-related neuropathic deficits in Hansen's disease in a "small fiber neuropathy" pattern that occurs in topography of a "temperature-linked" pattern

nasolabial fold and sparing of the deeper buccinator muscles produces a series of concentric creases extending out from the comers of the mouth (buccinator smile). As with further progression of facial nerve damage, complete lagophthalmos and ectropion of the eyelids develop and eyelashes may turn inward, abrading the cornea and leading to corneal scarring and ulceration.

### Small fiber nerve impairment-related clinical deficits

Since HD is a "small fiber neuropathy" preferentially affecting the unmyelinated and thinly myelinated Type C and A $\delta$  fibers, the "signature pattern" in the order of sensory loss is first warmth, followed by cold, pain, and finally touch sensation. The "temperature-linked pattern" of such NFI has been alluded to in the previous section. What is more pertinent for the clinician is to recognize the fact sensory loss is primarily intracutaneous and therefore not in the pattern of a typical "length-dependant" peripheral neuropathy. Furthermore, it is imperative to take cognizance of the neurological deficits that are not expected (*The Red Flags*) and that are entirely preserved in HD-related small fiber neuropathy such as position vibration sensation, superficial touch, and deep tendon reflexes.<sup>[22]</sup> Sensory impairment is characteristically intracutaneous and dissociative (pseudosyringomyelic neuropathy where temperature and pain are involved with the preservation of touch sensations) and precedes motor weakness.

### Motor clinical deficits

Motor deficits occur when the disease is advanced with the progression of the sensory loss. The nerves are also preferentially involved to those fibers closest to the surface of the body. Paralysis in the ulnar distribution appears first. The ulnar nerve is most affected over a 10–15 cm segment proximal to the olecranon groove, followed by the median nerve (claw hand), and finally, the radial superficial nerve at the wrist. In the lower extremities, the superficial segment of the peroneal nerve coursing laterally around the fibular head is infiltrated and enlarged causing foot drop. Intrinsic muscles of

the sole of the foot may also be involved by the affection of the segment of the posterior tibial nerve in the distal third of the leg. Figure 7 summarizes the clinical cutaneous and neurological examination findings in the typical Hansen's Disease.

## THE MANY FACES OF NEURO-HANSEN'S DISEASE

The typical neurodermatologic clinical picture of HD is well known and understood. Therefore, this section will dwell into the importance of the recognition of the “chameleons” (unusual, atypical, and heterogeneous presentations) and the “masqueraders” (mimickers) of HD. This approach is quintessential from a clinical standpoint, in “pattern recognition,” in the differential diagnosis, and leprosy neuropathy as a clinical dilemma in countries such as India where HD is highly endemic cannot be overemphasized. HD is eminently treatable and is absolutely essential that the treating physician should understand the “many faces” of neuro-HD. In the same token, the clinician should develop much certainty of the uncertainties of “masqueraders” of HD, hence preventing unnecessary long-term potentially toxic anti-leprosy medication.

### Pure neuritic leprosy

In 1903, Albert Neisser described a “neural type of leprosy/lepra nervorum” for the first time and added the same to the already accepted “nodular” and “anesthetic” forms of leprosy.<sup>[23]</sup> The Indian Association of Leprologists (IALs) included the distinct form of “neural leprosy” in their official six group classification in 1955 and named it “polyneuritic leprosy.”<sup>[23-25]</sup> In 1982, IAL renamed the nomenclature of “polyneuritic leprosy” as “pure neuritic type of leprosy.”<sup>[26]</sup>

India contributes to more than 50% of new cases detected globally every year. In the year 2011–2012, 127,000 new cases were diagnosed with an annual new case detection

rate of 10.35/100,000 of population. As on April 1, 2012, a total of 83,000 cases are on record with a prevalence rate of 0.68/10,000 population.<sup>[3]</sup> According to Indian data, PNL constituted about 4%–18% of leprosy patients and continues to occur in the postelimination era.<sup>[27]</sup>

The incidence is reportedly higher in South India comprising up to 18% of new cases. The most common presentation of PNL is a mononeuritis (single nerve involvement) or as asymmetrical mononeuritis multiplex which occurs in about 60% of the cases.<sup>[28,29]</sup> In a study done by the first author, it is documented that among the histological diagnosed cases on leprosy neuropathy from tertiary hospitals in Mangalore from 2010 to July 2017, PNL constituted 60% of cases.<sup>[30]</sup>

PNL is the variety where only manifestations of the peripheral nerve involvement are seen without any cutaneous lesions.<sup>[31]</sup> The challenge for the neurologists, dermatologists, and leprologists arises when typical characteristic cutaneous lesion described in the earlier section is absent. It can cause diagnostic dilemma with various peripheral neuropathies caused by infections, autoimmune diseases, nutritional deficiency, alcohol, toxins, and degenerative diseases. PNL is extreme type of leprosy, having good prognosis if picked up early on clinical screening, properly diagnosed, and treated effectively. Leprosy affecting the nerve solely or with concomitant skin lesions is not an uncommon condition in clinical practice. The ulnar, median, common fibular, tibial, facial, cutaneous radial, and major auricular are the nerves most frequently reported in different PNL studies. Neural thickening is frequent clinically; however, clinical nerve thickening is not a pathognomonic finding of leprosy neuropathy, which can be observed in compressive, inflammatory focal neuropathy, and even in hereditary neuropathies. Nerve abscesses may be formed due to severe inflammatory disease.<sup>[32]</sup> High-resolution ultrasonography (HRUS) through features of involved nerves such as nodularity, thickening (nerve cross-sectional area), fascicular echotexture, abscesses, long-segment involvement, and multiple nerve involvement<sup>[33,34]</sup> and the less invasive HRUS-guided fine-needle aspiration cytology (FNAC)<sup>[35]</sup> in clinically suspected PNL does provide a unique diagnostic tool.

In PNL, the deep sensation and deep tendon reflex impairment, as well as the presence of muscular weakness and amyotrophy, generally occur in advanced cases of prolonged evolution. It is responsible for extensive morbidity and often poses a diagnostic challenge. Most of these patients present with nerve function impairment (NFI as per the INFIR cohort study parameters) and usually present to the physicians or neurologists, as there are no skin lesions. A high degree of clinical suspicion is required for making the diagnosis of PNL. A wide range of differentials has to be considered as there are no absolutely diagnostic clinical features of leprosy neuropathy and thickening of nerves. Apart from the pattern of INFIR-NFA assessment abnormalities, SNC abnormalities, slit-skin smear (SSS), and exclusion of other potential neuropathic disorders, nerve biopsy (or FNAC of nerve) is the

TYPICAL NEURO-DERMATOLOGIC HANSEN's DISEASE	
<b>Sensory loss</b>	
Precedes weakness	
Dissociation (pin and temperature>position and vibration)	
Intracutaneous pattern	
<b>Motor involvement</b>	
ulnar=peroneal>median	
Preserved tendon reflexes	
Enlarged nerves	
Trophic changes	
Absorption of digits	
Positive findings on nerve or skin biopsy studies	

**Figure 7:** Sites of potentially palpable peripheral nerve enlargement in leprosy (Source: Figure 14.5 from Leprosy 2nd Ed. [1994], Hastings RC, Oromolla DVA [Editors])

gold standard for diagnosis of PNL. Immunohistochemistry and immunolabeling of lipoarabinomannan or PGL-1, ELISA anti-PGLI serology, and polymerase chain reaction (PCR) on nerve tissue will be helpful in confirming the diagnosis of PNL in acid-fast bacilli (AFB) negative material. The reader is referred to an exhaustive critical appraisal, case definition, assessment (serological, molecular, neurophysiological), and an algorithm for PNL diagnosis.<sup>[35,36]</sup>

### **Atypical, unusual presentations of lepromous neural involvement (The chameleon)**

To begin with, it is imperative to realize leprosy does manifest in various heterogeneous dermatological and neurological presentations. Hence, in an endemic country like India, we need to develop "*clinical pattern recognition skills*" to recognize the varied manifestations of leprosy.<sup>[37]</sup> The pleomorphic and unusual presentations of neural leprosy are summarized in Table 2.

A few of these varied unusual presentations will be discussed here. Nerve abscesses are uncommon presentations of leprosy or they may be reported rarely in PNL and paucibacillary (PB) disease. Another rare presentation is "symmetrical lepromous polyneuropathy" characterized by an early pan-sensory neuropathy.<sup>[38]</sup> This presentation belonged to the lepromatous with SSS positive and had severe and widespread involvement have a glove and stocking pattern of sensory loss, and many such patients did demonstrate a higher association of deformities and ulcerations. The pan-sensory NFI did produce proprioceptive loss, progressive sensory ataxia, pseudoathetosis of fingers, and generalized deep tendon areflexia. Electrophysiological studies demonstrated axonal

**Table 2: The many faces of Hansen's disease**

#### **Chameleons**

- PNL and nerve abscess
- CIDP presentation
- AIDP presentation
- Pseudosyringomyelic presentation-distal SFN
- Symmetrical "length-dependant" stocking-glove polyneuropathy-ataxic neuropathy
- Atypical cranial neuropathy-polyneuritis cranialis multiplex, Melkersson-Rosenthal syndrome, tic douloureux, bilateral optic neuropathy, vestibulocochlear, glossopharyngeal, vagus, and hypoglossal neuropathy
- CTS
- Isolated superficial ulnar nerve presentation
- Leprosy small fiber neuropathy-neuropathic pain, autonomic neuropathy aomplex complex regional pain syndrome
- Spinal cord (lepromous myelitis) and lepromous "ganglionitis"
- LLON
- Neurofibromatosis presentation

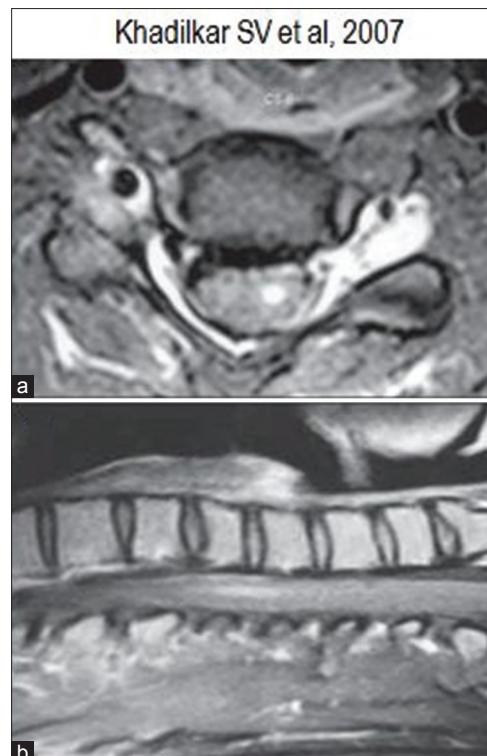
#### **Masqueraders**

- Tangier's disease
- Neurofibromatosis

PNL: Pure neuritic leprosy, CIDP: Chronic inflammatory demyelinating neuropathy, AIDP: Acute inflammatory demyelinating neuropathy, SFN: Small fiber neuropathy, CTS: Carpal tunnel syndrome, LLON: Lepromous late-onset neuropathy

neuropathy with proximal conduction abnormalities in F wave and H reflex studies. The interpretation of abnormalities in F and H reflex is speculated to indicate additional proximal affection of the neural pathway in patients of leprosy having sensory ataxia with proprioceptive loss. In this study, a 20-year-old male was reported with left upper extremity mononeuritis multiplex, who later developed lightning pain in the medial arm and nape of the neck with pan-sensory loss including kinesthetic sensations. The nerve biopsy was positive for acid-fast lepra bacilli by Fite-Faraco Stain. Surprisingly, the cervical spine gadolinium-based-magnetic resonance imaging (MRI) exhibited abnormalities to suggest an expansive focal spinal granuloma, with gadolinium intramedullary cord signal inflammatory changes at C5C6 levels and dorsal root ganglionitis [Figure 8]. This case from India and another case report from Brazil reflected yet another unusual presentation of HD as lepromous myelitis with dorsal root ganglionitis.<sup>[39-41]</sup>

Leprosy late-onset neuropathy (LLOH) is an uncommon delayed-onset painful multiplex neuritis or polyneuropathy (neuropathic pain and burning feet) occurring in patient ruled out to harbor concurrent etiologies of neuropathy but who have had a history of leprosy (one to two decades ago) successfully treated with MDT.<sup>[42]</sup> Recently in 2013, LLOH presenting as an ataxic presentation was documented. From Saint-Malo, France, a delayed immune reaction is said to explain the late appearance of LLON due to the persistence of the bacillus



**Figure 8:** (a) T1W postcontrast axial image of the cervical spine at C5-6 showing evidence of ganglionitis and spinal cord. (b) T1W postcontrast sagittal MRI of cervical spine showing intramedullary hyperintensity with cord swelling

antigens.<sup>[43]</sup> Treatment with prednisone was associated to great improvement of the neuropathic pain.

Painful small fiber neuropathy in leprosy is another rare but well documented clinical phenotype consisting of Type A $\delta$ -mediated neuropathic pain in multibacillary (MB), Type 2 leprae reactions, and PB (including PNL) patients. This condition also presents as complex regional pain syndrome Type 2 (CRPS/Sudeck's dystrophy).<sup>[44]</sup> This phenotype is a disabling and indeed painful condition compromising of a triad of autonomic, sensory, and motor symptoms disproportionate to the inciting event. In accordance with the INFIR cohort study, such small fiber (Type C and A $\delta$ ) neuropathy could be detected by QST, and additional specialized test such as contact heat-evoked potentials for the assessment of somatosensory pathways, and by studying the abnormalities of unmyelinated fibers in the cornea using corneal confocal microscopy. Autonomic neuropathy in leprosy is regional and manifested by disturbances in sweating (starch-iodine test), triple axon reflex, and vasomotor reflexes as detected by histamine test and digital laser color Doppler flow velocimetry.<sup>[29]</sup>

Apart from the relatively more common facial and trigeminal nerve involvement, atypical cranial neuropathies, such as polyneuritis cranialis multiplex, Melkersson–Rosenthal syndrome (triad of recurrent facial palsy, lingua plicata, and facial edema), tic douloureux, bilateral optic neuropathy (resulting from Type I leprae reaction), vestibulocochlear, glossopharyngeal, vagus and hypoglossal nerve palsy have been reported as one of the unusual neural presentations of HD<sup>[45]</sup> and hence does emphasize the need for extra vigilant and meticulous neurological examination at the bedside.

Miscellaneous modes of rare presentations of neuro-HD described in the literature include chronic inflammatory demyelinating neuropathy (CIDP)<sup>[46,47]</sup> and acute inflammatory demyelinating neuropathy (AIDP).<sup>[48-50]</sup> The Korean CIDP case report proved the etiology to be *M. leprae* by nerve biopsy (Fite Faraco stain, teased fiber preparation, and immunohistochemistry; and ultrastructural nerve study demonstrating AFP in unmyelinated SCs). However, in this case, the clinical clue for HD was the preservation of deep tendon reflexes.

The second single CIDP case report from Brazil in a 52-year-old satisfied the cerebrospinal fluid criteria of albuminocytological dissociation and the NCS showing demyelinating sensory-motor polyradiculopathy consistent with CIDP. This presentation responded well to pulse-methylprednisolone/prednisolone therapy that plausibly could be attributed to cell injury caused by type 1 reaction that exposed the neural antigens and incited an autoimmune reaction (leprae type 1 reaction).

AIDP-like presentations described in Indian literature were due to Type 2 lepra reaction.<sup>[48,50]</sup> Rarely, cases have been known that present as AIDP without any evidence of lepra reaction and two case reports of such occurrence does exist in the Indian literature.<sup>[49]</sup>

It is intriguing to answer the puzzling question "*Is the CNS involved in HD?*" Autopsy studies have identified *M. leprae*-specific antigens – PGL-1 and DNA in peripheral nerves/SCs even in the central nervous system (CNS)-medulla oblongata (nucleus ambiguus/hypoglossal nucleus) and spinal cord AHC motor neurons (cervical, thoracic, and lumbar cords).<sup>[51]</sup> A case report from Korea<sup>[52]</sup> provides first report demonstrating histopathological and molecular evidence for CNS involvement by *M. leprae* in a living patient. The report describes a 69-year-old male presenting with mild facial palsy on the left side. His history was remarkable for the diagnosis and MDT for borderline leprosy 3 years ago. An MRI brain was done as a part of the investigation for his left facial palsy. Brain MRI demonstrated a 2-cm nonenhancing cystic lesion with perilesional edema in the right frontal lobe. Based on the presumptive diagnosis of low-grade glioma, a neuronavigation-guided craniotomy and tumor resection was done. Histopathological, immunohistochemistry examination and nested PCR of the brain specimen were positive for *M. leprae*. The plausible explanations for entry of *M. leprae* to the CNS may be due to disrupted blood-brain barrier, hematogenous entry of *M. leprae* to the dorsal root ganglion cells.<sup>[53,54]</sup>

### **Mimickers of leprous neural involvement (*The masqueraders*)**

This can be well exemplified by the fascinating case report from NIMHANS reported in 2004.<sup>[55]</sup> This case report demonstrates the clinical acumen of the examiner to abide by the Occam's razor for clinical diagnosis. The report describes a 30-year-old Indian male who had presented with a chronic indolent mononeuritis multiplex and trophic ulcers of 16-year duration. His neurological picture comprised of hypopigmented macular patches over the abdomen and a large nonhealing burn wound over the left forearm, bilateral facial weakness, and asymmetrical wasting of small muscles in the hands. Pain, touch, and temperature sensations were impaired over hands, the face, chest, back, abdomen, and proximal third of the thigh without any clinical evidence of nerve thickening. Nerve conduction studies revealed features of demyelinating neuropathy. A "split skin" smear for lepra bacilli was negative.

The clinical clues not in favor of HD was the progression of neurological deficits while on MDT, the presence of splenomegaly (ignored earlier as tropical splenomegaly syndrome), fatty liver, thrombocytopenia, undetectable levels of high-density lipoproteins (HDL) and low-density lipoproteins (LDL), and preservation of deep tendon reflexes. The low levels of apolipoprotein A1 (ApoA1) and undetectable levels of HDL and LDL levels pointed to a lipoprotein neuropathy known as Tangier's disease. Biopsies of the sural nerve and skin showed striking vacuolation of SCs and myelin sheaths, and foamy vacuolated fibroblasts, respectively, and no evidence of HD. Abnormal lipid deposition in SCs is proposed to be responsible for the neuropathy. This masquerader of HD in a country such as India where HD is highly endemic cannot

be better exemplified as an “unforgettable clinical lesson” for the astute physician, dermatologist, and/or neurologist.

## THE DERMATOLOGICAL PERSPECTIVE

### Diagnostic challenges

Cutaneous manifestations of leprosy depend on the spectrum, in which the patient has been when the detection occurred. Host cell-mediated immune response toward the bacilli determines the morphology of the skin lesions. Traditional classification according to the Ridley–Jopling scale includes tuberculoid leprosy, borderline leprosy, and lepromatous leprosy. Other types such as indeterminate and PNL represent further diversity in the spectrum of leprosy.<sup>[56,57]</sup>

Tuberculoid leprosy represents a sufficient cell-mediated immune response where there could be one or few hypopigmented, erythematous, and anesthetic macules with a raised margin.<sup>[58]</sup> Usually, a local nerve trunk is enlarged. This type of leprosy is generally detected early due to the conspicuous skin lesions with dyschromia (hypopigmentation or erythema), dysmorphia (plaque formation), anesthesia, asteatosis (dryness due to autonomic dysfunction), and alopecia (hair loss) [Figure 9a and b]. However, such lesions can be seen in many infectious and noninfectious dermatological diseases such as early vitiligo, pityriasis versicolor, granuloma annulare, psoriasis, sarcoidosis, cutaneous tuberculosis (lupus vulgaris), chromoblastomycosis, tinea corporis, and erythema chronicum migrans (Lyme disease) [Figures 10a-f]. Presence of anesthesia is an important distinguisher from the other dermatoses however sometimes certain office diagnostic procedures or a skin biopsy/histopathology may be required. Skin smear for AFB is negative in tuberculoid leprosy. Indeterminate leprosy represents early leprosy with hypochromic lesions with indefinite borders which may cause serious diagnostic challenges with many hypopigmented skin lesions.

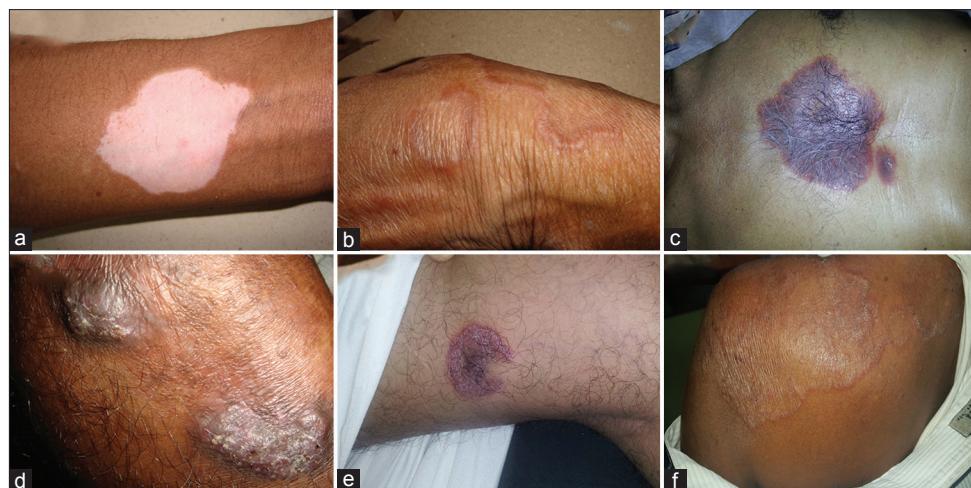


**Figure 9:** (a) Hypopigmented slightly elevated plaque of tuberculoid leprosy. (b) Erythematous well-defined annular plaque of tuberculoid leprosy

Borderline leprosy is the spectrum, in which vast majority of the cases fall. This is the immunologically unstable variety that may climb up or down in the immune spectrum depending on the host defense. Higher immune status is represented by the borderline tuberculoid disease and as the cell-mediated immunity declines the mid-borderline and borderline lepromatous disease will ensue. This variety of leprosy is also prone for lepra reactions.<sup>[59]</sup> Lesions of borderline leprosy vary from a few macules or plaques to multiple nodules and infiltrations. Borderline tuberculoid leprosy is characterized by large or multiple erythematous or hypopigmented plaques with less distinct margins and often with satellite lesions [Figure 11a]. Mid-borderline leprosy presents with more numerous asymmetrical lesions and often typical annular, erythematous, indurated plaques with sharply punched out inner margins with sloping outer margins giving a “Swiss-cheese” appearance<sup>[60]</sup> [Figure 11b]. Because of this variety of morphology, a number of diseases such as leishmaniasis, secondary syphilis, psoriasis, lymphoma, and sarcoidosis may be considered among the differential diagnosis [Figure 11c and d]. In borderline lepromatous leprosy, there are numerous macules, nodules, and plaques that tend to get symmetrical [Figure 12a]. Multiple peripheral nerves are often asymmetrically enlarged. Variable sensory impairment is observed.

Lepromatous leprosy a disease subtype that occurs in very-low immune status against the *M. leprae*. The disease is characterized by symmetrically distributed macules, papules, nodules, and diffuse infiltrative lesions [Figure 12b]. Hence, it can resemble many generalized inflammatory and infective and noninfective diseases as with borderline lepromatous leprosy. Infiltration of earlobe and sometimes nose may resemble sarcoidosis, relapsing polychondritis, and rhinophyma.<sup>[61]</sup> Bilateral pedal edema can be a manifestation of lepromatous leprosy, and it can compete with many medical illnesses for the diagnosis.<sup>[62]</sup> Histoid leprosy is a distinct form of leprosy that manifests as multiple, discrete, smooth, painless, firm skin-colored nodules, and papules on apparently normal skin [Figure 12c]. Similarly, nonnodular diffuse infiltrative disease, the “Lucio leprosy” may also be a rare presentation<sup>[63]</sup> [Figure 12d].

Reactions in leprosy (lepra reactions) are the immunologically mediated inflammatory episodes due to the presence of *M. leprae* or its antigens in the tissues. Type 1 lepra reaction is usually seen in the borderline spectrum (usually borderline tuberculoid) of the disease and usually occurs within 3 months of the initiation of the treatment of leprosy.<sup>[64]</sup> It is a delayed type of hypersensitivity characterized by edema and ulceration of existing lesions; edema of the face, hands, and feet; and tender nerves due to acute neuritis [Figure 13a]. Among the skin disease simulating type 1 reactions are urticaria, cellulitis, Well’s syndrome (eosinophilic cellulitis), lupus erythematosus, and drug eruptions. Type 2 lepra reaction is usually seen in the lepromatous or borderline lepromatous spectrum of the disease. It is often described as



**Figure 10:** Differential diagnosis for tuberculoid leprosy. (a) Vitiligo. (b) Granuloma annulare. (c) Psoriasis. (d) Cutaneous tuberculosis. (e) Chromomycosis. (f) Tinea corporis



**Figure 11:** (a) Erythematous plaques of borderline tuberculoid leprosy with satellite lesions. (b) Mid-borderline leprosy showing erythematous plaque with sharply punched out inner margins with sloping outer margins ("Swiss cheese"). (c) Secondary syphilis. (d) Sarcoidosis

an immune-complex-mediated condition with T-cells further complicates the immunopathology.<sup>[65]</sup> Cytokines such as TNF- $\alpha$  and others are elevated. It presents with appearance of recurrent painful subcutaneous erythematous nodules (erythema nodosum leprosum [ENL]) that can ulcerate [Figure 13b]. There may be signs of systemic impairment such as fever, lymphadenitis, neuropathy, arthritis, orchitis, iritis, and other organ inflammation.<sup>[66]</sup> (Guerra) It has a chronic and relapsing course. Due to its multiorgan nature of the disease, it simulates many diseases in the field of rheumatology, ophthalmology, internal medicine, and dermatology.

## RECENT ADVANCES IN DIAGNOSTIC ARMAMENTARIUM OF HANSEN'S DISEASE

Although HD has been described since antiquity, it is imperative to take cognizance of the recent advances in the diagnostic armamentarium when either a neurologist or dermatologist



**Figure 12:** (a) Borderline lepromatous leprosy. (b) Nodules of lepromatous leprosy on the pinna. (c) Histoid leprosy showing skin-colored nodules over a normal looking skin. (d) Diffuse infiltrative "Lucio" leprosy

is faced with clinical diagnostic dilemma as HD is a "great imitator" with many faces of presentations as illustrated.

Biopsy is considered as the gold standard investigation for diagnosing HD. The nerve biopsy in subacute and chronic neuropathies is clearly indicated only in two distinct clinical scenarios (i) suspected vasculitides with or without the clinical features of neuropathy and (ii) clinically established neuropathies of unknown cause on a neuropathy workup. Nerve conduction studies are vital to the workup of a patient with vasculitis for two reasons: (i) nerve conduction study can potentially detect asymptomatic peripheral neuropathy and (ii) abnormal sural (dorsal ulnar cutaneous, superficial radial, and superficial peroneal nerve) is a prerequisite to the demonstration of vasculitis in nerve biopsy. Another noninvasive method of nerve histopathological assessment, especially when cutaneous features of HD are evident is sensory cutaneous nerve FNA, rather than a nerve biopsy. FNAC neither requires infiltration by local anesthesia required and



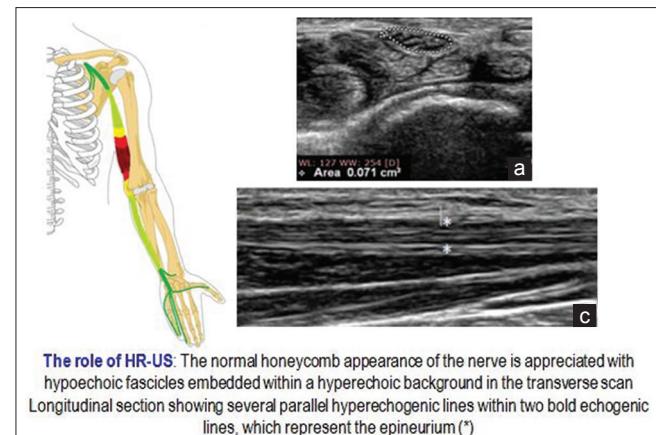
**Figure 13:** (a) Type 1 lepra reaction showing edematous ulcerated plaque on the face. (b) Erythema nodosum leprosum (ENL), the cutaneous lesions of type 2 lepra reaction. (c) Partial claw hand deformity

nor are the fascicles stripped from the nerve bundle; there is also no need for removal of a wedge from a nerve.<sup>[67]</sup>

As a clinician, it is prudent to note that nerve biopsies may be not clinically helpful in 50% cases and in PNL cases when AFB is negative. In the field of laboratory-based diagnosis of HD, as a newer approach to increase the likelihood of detecting HD in skin punch biopsies and/or nerve biopsy is the combination of Fite–Faraco staining with multiplex PCR.<sup>[68]</sup>

Conventionally, peripheral nerve lesions are diagnosed on the basis of clinical history, physical examination, and electrophysiological studies. An HRUS is an adequate and cost-effective noninvasive method for evaluating peripheral nerve disorders.<sup>[69]</sup> The anatomic location, the loss of normal honeycomb appearance of the nerve, altered cross-sectional area, unique pattern of nerve enlargement of the nerve involved, intraneuronal Doppler vascularity, the different types of abnormal nerve fascicular echo pattern, intraneuronal abscess, and echo appearance of the perineurium and epineurium provide an accurate information to the clinician to the possible etiology of nerve pathology, selection of nerve for FNAC or biopsy, and for selecting the appropriate treatment. We stress that HRUS pattern of unique nerve enlargement (ulnar nerve above medial epicondyle) could help, especially in diagnosing PNL, in which skin lesions are absent, useful in screening asymptomatic household contacts (SN) with leprosy, and is also useful to differentiate leprosy from other neuropathies, in which nerve enlargement can occur [Figure 14].<sup>[70]</sup>

Using newer imaging technology, conventional MRI, MR neurography (MRN), diffusion MRN, and diffusion tensor imaging tractography to delineate and study the various pathological correlates of HD provides a precise imaging of the nerves involved and helps in obtaining a microbiological diagnosis, especially so in PNL.<sup>[71]</sup>



**Figure 14:** The role of high-resolution ultrasonography in characterizing leprosus neuropathy

## THERAPEUTIC CHALLENGES

Leprosy has been one of the earliest diseases to be proven of infectious etiology, and hence there has been a constant search for an ideal chemotherapy. Although there have been a number of drugs used historically, it was Dapsone in 1941 that revolutionized the therapy.<sup>[1]</sup> In early 1960s, dapsone resistance was detected, but the era of MDT began only in 1980s. The WHO recommended that all patients with leprosy should receive combination of rifampicin, clofazimine, and dapsone.<sup>[72]</sup> For the purpose of therapy, leprosy has been divided into a PB and MB. PB leprosy is a case that has 5 or less skin lesions, single nerve trunk lesion, or smear positive for AFB and MB leprosy represents the vice versa. Accordingly, PB patients receive 600 mg rifampicin monthly and 100 mg dapsone daily, for 6 months. MB cases are treated with 600 mg rifampicin and 300 mg clofazimine monthly, and 100 mg dapsone and 50 mg clofazimine daily for 12 months. There are many reserve drugs in the treatment of leprosy such as ofloxacin, minocycline, and clarithromycin which are used where there is resistance or intolerance to the regular drugs. Single-lesion PB patients can be treated with a single therapeutic dose consisting of 600 mg rifampicin, 400 mg ofloxacin, and 100 mg minocycline.<sup>[73]</sup>

Lepra reactions are therapeutic challenge. Severe type 1 reaction should be considered as a medical emergency because it shall be recognized early and treated with systemic corticosteroids to prevent muscle paralysis due to acute neuritis. Type 2 lepra reactions are generally chronic and skin lesions appear in crops often triggered by certain stimuli such as intercurrent illnesses, surgeries, pregnancy, lactation, menstruation, trauma, or mental stress.<sup>[74]</sup> Corticosteroids and thalidomide are the mainstays of treatment, but other immunosuppressants such as azathioprine, clofazimine, and cyclosporine have also been used. Some cases of ENL are highly refractory to almost all therapies and with high morbidity or mortality.<sup>[75]</sup>

Leprosy is a disease that is known historically for its disabilities and deformities as a sequela or complications. Complications

may be directly related to the disease due to the invasion of the bacteria (e.g., leonine face), due to motor paralysis (claw hand, foot drop), or sensory loss (e.g., plantar ulcers) [Figure 13c]. It can also cause blindness, bone defects, and sexual dysfunction.<sup>[76,77]</sup> Limitation of disabilities due to leprosy was an uphill task in the predapsone era and the monotherapy, but the current MDT and control programs have significantly limited the deformities.

## CONCLUSION

At the end of this review, separating the pearls from the oysters, HD is indeed riddled with clinical and diagnostic challenges. Hence, "in the era of leprosy eradication," there must be a renewed impetus for enhanced global strategy for further reducing the leprosy burden and sustaining leprosy control activities in addition to early diagnosis and prompt treatment to prevent impairment, deformity, and disability ("Morbidity control"). The detection of "silent neuropathy" and "contact screening" needs to be underscored. Lastly, a "multidisciplinary awareness" of the "different faces of HD," the neurodermatologic perspectives, and advances in the noninvasive investigative tools is mandatory among the allied specialties such as dermatologists, leprologists, neurologists, ophthalmologists, otolaryngologists, orthopedic surgeons, and rheumatologists.

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## Conflicts of interest

There are no conflicts of interest.

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