REVIEW

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Diagnosis and treatment of leprous neuropathy: a review

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ABSTRACT

One significant subset of curable neuropathies brought on by *Mycobacterium leprae* is leprous neuropathy. Millions of people in most underdeveloped nations suffer from leprous neuropathy, which can lead to debilitating motor deficiencies, sensory loss, and skin deterioration. The peripheral nerve system and skin are the primary organs affected by leprosy. The clinical characteristics, cutaneous histology, and bacteriology may all be used to conclude the diagnosis. Leprosy neuropathy diagnosis also requires a nerve biopsy. Needles electromyography and nerve conduction investigations are two examples of electrophysiologic nerve examinations. Both studies offer details on the degree of nerve involvement, the location of lesions, and the underlying mechanism of injury. For patients with leprosy neuropathy, multiple medication therapies are recommended. Aside from standard medical care, acute neuropathy may sometimes require surgical intervention. In reversal reactions, corticosteroids can prevent or lessen nerve damage.

Keywords: Diagnosis, leprosy, leprous neuropathy, treatment.
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INTRODUCTION

Several underdeveloped nations continue to have millions of people who suffer from leprous neuropathy, which is brought on by *Mycobacterium leprae* infection of nerve cells. Leprosy is still a serious health issue in many parts of the world. India, Brazil, Indonesia, and Nigeria have the most frequent cases.[1] In developed nations, where leprosy is still uncommon and often underestimated, new instances of the disease are frequently found due to rising migration.[2]

The peripheral nervous system and skin are the two organs most commonly impacted by leprosy, followed by the upper respiratory tract, eyes, and bones, which occur less frequently. Usually, this condition causes a low mortality rate, but peripheral neuropathy becomes a major morbidity, which frequently results in impairments and deformities. The myelinating and non-myelinating Schwann cells can be invaded and overgrown by Mycobacterium leprae, a remarkable ability. Motor deficiencies were less frequent than sensory loss.[1,3–5]

Based on Ridley Jopling's Morbus Hansen classification, leprosy is classified as tuberculoid, borderline tuberculoid, indeterminate, mid borderline, borderline lepromatous, or lepromatous. On the other hand, the WHO classified paucibacillary (PB) and multibacillary (MB).[6] One of the following cardinal signs of leprosy is required to be considered a case of leprosy, according to the WHO Expert Committee on leprosy: an erythematous or hypopigmented skin patch accompanied by loss of sensation, an enlarged or thickened peripheral nerve accompanied by loss of sensation and/or muscle weakness in associated nerve supply, and slit-skin smear (SSS) shows positive result of acid-fast bacilli.[7] Laboratory work is still lacking in leprosy diagnosis. Only classification, follow-up, and the diagnosis of relapse are the currently available tests.[8] The right medication, limiting one's impairment, and rehabilitation are the main components of leprosy management.[9] This review aimed to improve our knowledge about diagnosing and treating leprous neuropathy.

LEPROUS NEUROPATHY DIAGNOSIS

The upper respiratory tract, peripheral nerve, and skin are the main targets affected by leprosy. Typically, skin lesions are the first observable symptom. Neuropathies are a crucial component of leprosy's manifestations. Leprosy neuropathies can take on a variety of shapes and forms. Leprosy's major morbidity is peripheral neuropathy, which can harm motor, sensory, and autonomic nerves. At the time of diagnosis, between 30 and 60% of individuals will have nerve injury. Multiple mononeuropathies are a common diagnosis in patients and are frequently seen in specific nerve involvement.[8–10]

M. leprae usually infects distant body parts because Hansen's neuritis has thermotropism for cooler locations. As a result, it is predicted that proximal, deeper, and warmer locations will be spared. A study with 396 newly diagnosed patients dominated by ulnar nerve involvement, with both motor (20%) and sensory (17%) components being impacted. The median sensory nerve was damaged in 8.8% of cases. In another study, experts found six median neuropathy and posterior tibial nerves usually damaged as well.[10,11]

Usually, diagnosis of leprosy found no difficulty, especially in the endemic area. However, if there is no skin lesion encompassing a polyneuropathy, diagnosis becomes more challenging.[12]

Detecting their presence requires great skill and experience, without which the diagnosis may be overlooked or delayed. It is important because nerve fibrosis may cause permanent impairment and physical deformities.[3,13]

World Health Organization defines leprosy as a person with one of the following cardinal indications of leprosy: loss of sensation in an erythematous or hypopigmented skin patch, an enlarged or thickened peripheral nerve accompanied by sensory loss and/or muscle weakening supplied by the nerve, as well as the detection of acid-fast bacilli by SSS.[7,9] The following procedures can be used to test the cardinal signs mentioned below.

Skin Biopsy of Epidermal Nerve Fiber

In small fiber sensory neuropathy, intraepidermal nerve fibers (IENF) quantification is the standard diagnostic tool. This modality can evaluate an autonomic nerve in the hand and feet to find nerve involvement and improvement during and after multidrug therapy.[7,9]

Neurophysiological Evaluation

Ballpoint tests or tactile sensitivity evaluation using Semmes-Weinstein MFT, quantitative skin tests, nerve conduction studies, and voluntary muscle tests are several nerve workups for leprosy neuropathy. Usually, electrophysiological recording can be done in the ulnar, radial, tibial, median, and common peroneal nerve.[7]

Evaluating the conduction of the nerve is critical in leprosy, especially in the pure neuritic form. Previous research has shown that nerve conduction tests can detect nerve dysfunction far sooner than symptoms and as an indicator of nerve function impairment. It may also be useful to evaluate loss of sensation or weakness in the distribution of the studied nerve, albeit these are not always evident.[8,14]

In nerve conduction studies of leprosy, primarily axonal neuropathy is characterized by a decrease in compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitude. Sensory nerves are impacted more frequently than motor nerves, and SNAP amplitudes are usually altered more than CMAP. Warm detection thresholds (WDT) were shown to be the most frequently impacted by QST, followed by nerve conduction. These two modalities detect nerve abnormalities up to 12 weeks before MFT becomes aberrant. When compared to paucibacillary leprosy, patients with multibacillary leprosy experienced much more severe alterations in nerve conduction characteristics. In both groups of patients, the lower extremities were more commonly and seriously implicated than the upper limbs.[7]

Nerve conduction investigations and needle electromyography are examples of electrophysiologic nerve examinations. Both examinations provide information on the extent of nerve involvement, lesion distribution, and mode of injury.[15] Electrophysiology is also used to evaluate the toxicity of medications such as dapsone and thalidomide. This modality should not be used as a diagnostic and only be useful in assessing the extent of nerve involvement.[9,16]

High-resolution Ultrasonography with Color Doppler (HFUS CD)

This modality can describe changes in leprosy neuropathy, such as increased intraneural or perineural vascularization, nerve thickening at entrapment sites, and cross-sectional area differences between lepromatous and tuberculoid. On the other hand, infrared thermography and laser Doppler are the other modalities to evaluate autonomic fiber involvement.[7]

High-frequency ultrasound (12-18 MHz) and color Doppler can be used in median, ulnar, and common fibular nerves. Ultrasonography is an objective modality to evaluate increasing vascularity, distorted echo texture, and enlargement in nerve damage. Abnormal nerves usually show hyper or hypoechoic area or focal thickening with loss of normal fascicular pattern. Non-palpable sites can also evaluated by ultrasonography, and experts may find details of thickening, nerve edema, micro abscess, and fascicular architecture alteration. Compared to magnetic resonance imaging (MRI), ultrasonography is less expensive, widely accessible, can be done at the bedside, and is more rapid.[9]

Magnetic Resonance Neurography (MRN)

Pure neuritic neuropathy with single-nerve involvement may benefit from this modality. Magnetic resonance neurography can demonstrate the presence of nerve thickening, edema, and micro abscess in the peripheral nerve, as well as the combined involvement of lumbosacral and brachial plexuses.[9,11] In T2-weighted images, leprosy nerves show classic diffuse nerve expansion, increased signal intensity, and nodular enhancement. Specific abnormalities such as nerve calcifications may be observed in the subacute and chronic periods. The MRN has also been used to describe the involvement of the brain and spinal cord in addition to peripheral nerves.[9]

Nerve Biopsy

The biopsy site is chosen based on clinical and electrophysiological abnormalities.[9] Typically, a branch of the radial cutaneous nerve near the wrist or a branch of the sural nerve immediately above the ankle is chosen for biopsy. A cutaneous nerve next to the skin may be chosen for biopsy if it is enlarged, especially in tuberculoid. A nerve biopsy collected from a tiny cutaneous or subcutaneous nerve can be used to identify pure neural leprosy. Bacteriology and cytology using PCR can also be done in fine needle aspiration samples from bigger nerves.[4,7,8] For routine analysis, nerve tissue is stained with Kulchitsky Pal for myelin, hemotoxylin, eosin for hemotoxylin, and Fite-Faraco for lepra bacilli. Transmission electron microscopy, semi-thin sections, and teased-fiber preparation are special techniques to evaluate leprosy neuropathy histology.[9]

The spectrum of pathological alterations in the skin is reflected in nerves depending on the host's immunological response. At the tuberculoid, epithelioid granulomas with no or few AFB are found. On the other hand, AFBs are common in lepromatous, accompanied by macrophage and plasma cell infiltrates. Additional nerve abnormalities include perineural edema, fascicle involvement, fiber density reduction, and regions of demyelination.[9]

Extensive research has been conducted to determine the ideal method for leprous neuropathy screening. Ballpoint pen-

Table 1. WHO recommendation in 2017[9]

Drug	Dosage	Administration	Duration of treatment	
			Paucibacillary	Multibacillary
Dapsone	100 mg	Daily	6 months	12 months
Clofazimine	50 mg	Daily		
Rifampicin	600 mg	Monthly		
Clofazimine	300 mg	Monthly		

Table 2. The treatment for drug-resistant leprosy[9]

Duration	Medications	
	Rifampicin resistance	Rifampicin with ofloxacin resistance
First 6 months (daily)	Ofloxacin 400 mg + Minocycline 100 mg + Clofazimine 50 mg	Clarithromycin 500 mg + Minocycline 100 mg + Clofazimine 50 mg
Next 18 months (daily)	Ofloxacin 400 mg OR Minocycline 100 mg + Clofazimine 50 mg	Clarithromycin 500 mg OR Minocycline 100 mg + clofazimine 50 mg

*Ofloxacin 400 mg can be replaced by levofloxacin 500 mg OR moxifloxacin 400 mg

testing (BPT), 10 g Semmes–Weinstein monofilament (SWM), moving two-point discrimination, pinprick, position sense, vibration sense, quantitative thermal, voluntary muscle, nerve palpation, and nerve conduction studies are some of the screening modalities that have been evaluated.[17] Slit skin smears and electrophysiological examination are performed on all patients, followed by skin biopsies if SSS is negative. When the diagnosis of pure neuritic leprosy is questionable, ultrasonography and MRN investigations are used to select the site of nerve biopsy. When no other findings are available in pure neuritis leprosy, a fascicular nerve biopsy is performed. In a research setting, serological and molecular markers are mostly used.[9]

MANAGEMENT

Aims in leprosy management are appropriate pharmacotherapy, disability limitation, and rehabilitation. Patient and family education can be useful in reducing impairment, controlling droplet spread, and preventing close contact.[9]

Multidrug Therapy Based on the World Health Organization

Multidrug therapy is effective in curing bacterial infection, and the newest recommendation suggests three drugs for all leprosy patients (Table 1).[9]

Dapsone is a bacteriostatic and weak bactericidal medication that is used daily. Dapsone has been demonstrated to decrease *M. leprae* proliferation. In G-6PD deficient patients, it can cause hemolysis, reversible neuropathy, and dose-dependent methemoglobinemia. Blood count should be done to evaluate hemolysis before starting treatment and evaluation after six weeks.[7,9]

Rifampicin is a monthly regimen and has a bactericidal effect. Recurrence, either re-infection or re-activation, does occur occasionally. Throughout therapy, the hepatic function must be monitored.[7,9]

Drug-Resistant Leprosy

Multidrug failure, relapsing cases, and drug-resistant strains of *Mycobacterium leprae* have recently increased.[18] Rifampicin is a highly successful MDT agent, yet several countries report cases of quinolone resistance among new and previously treated patients. The WHO recommends using second-line bactericidal medications such as minocycline and clarithromycin (Table 2).[9]

Corticosteroids

Corticosteroids are one of the primary treatments for subclinical neuropathy or neuritis in leprosy. This drug works by reducing acute inflammation and decreasing pain. This agent usually starts at 40 mg daily and is tapered off slowly over 6 months. There is no strong evidence to support corticosteroids' long-term benefit in improving nerve function. However, long term treatment with corticosteroids may be useful to prevent leprosy.[9] New treatments for leprosy neuropathy are desperately needed.[7]

Lepra Reaction

Thalidomide does not affect type 1 lepra response. On the other hand, glucocorticoids, such as prednisone with an initial dose of 40-60 mg/day, are the most effective treatment for type 1 reactions. The glucocorticoid dose can be decreased as the inflammation diminishes but must be continued for at least 3-6 months. In mild erythema nodosum leprosum, a patient can be treated with antipyretic alone, but in most cases, additional treatment is needed. Severe cases with systemic involvement may benefit from corticosteroid therapy.[9]

Neuropathic pain

The nerve function may improve with prednisolone, and a low-dose regimen can reduce the incidence of nerve impairment. World Health Organization recommends prednisolone 40 mg and tapered down in 12 weeks for acute neuritis. Long-term use of corticosteroids raises the risk of significant morbidity from these medications' adverse effects. Therefore, clinicians may use steroid-sparing medicine such as methotrexate.[7,9]

Pregabalin (75–150 mg one to three times daily), gabapentin (100–300 mg two to three times daily), clonazepam (0.5 to 2 mg two to three times daily), duloxetine (20–60 mg two to three times daily), nortriptyline (25 mg one to two time daily) and amitriptyline (5–25 mg daily) could be used as adjunct medications. Those tricyclic antidepressants and anticonvulsants can be used to control

chronic neuropathy in leprosy patients but have no protective effect on nerve deterioration.[9,19]

Rehabilitation And Physical Therapy

Rehabilitation can start at diagnosis and continue until the patient reaches normal life. A comprehensive rehabilitation program may include physical therapy, surgical procedures, vocational activities, and assistive devices.[9] World Health Organization recommends splinting and resting the affected limb if possible.[7] It is also critical to record monofilament and muscle power to assess nerve activity.[9] Different assistive devices and properly constructed splints considerably improve daily activity performance. Occupational and community-based interventions are also needed.[9]

Surgical Options

Despite the finest medical care, neuropathies can result in irreversible nerve injury and deformity. Acute nerve abscess drainage, neurolysis, and decompressive surgery are recommended once corticosteroid therapy fails. Reconstructive surgery to fix defects may increase the quality of life and minimize leprosy stigma.[9]

Non-Pharmacological for Neuritis

Management, such as applying moisturizer and oil to prevent dry skin, may also avoid superficial wounds.[7]

CONCLUSION

It is important to understand leprosy neuropathic symptoms and diagnosis. Appropriate diagnosis and therapy are needed to avoid morbidity and preserve patients' normal life.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to this article.

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