

Understanding Demyelination in Leprosy Neuropathy: A Nerve Biopsy Analysis

Sir,

The nerve biopsy changes in leprosy neuropathy range from well-formed granuloma in the tuberculoid form to the presence of foam cells and high bacillary load in lepromatous forms. The nerve damage in the tuberculoid and borderline leprosy is due to the severe axonal loss caused by extensive

endoneurial inflammation and granuloma which destroy the neural architecture. On the other hand, the nerve damage in lepromatous and borderline lepromatous (BL) cases has been attributed to demyelination caused by direct Schwann cell damage by bacilli, macrophage-induced myelin toxicity and also an immune attack on Schwann cells. The nerve biopsies

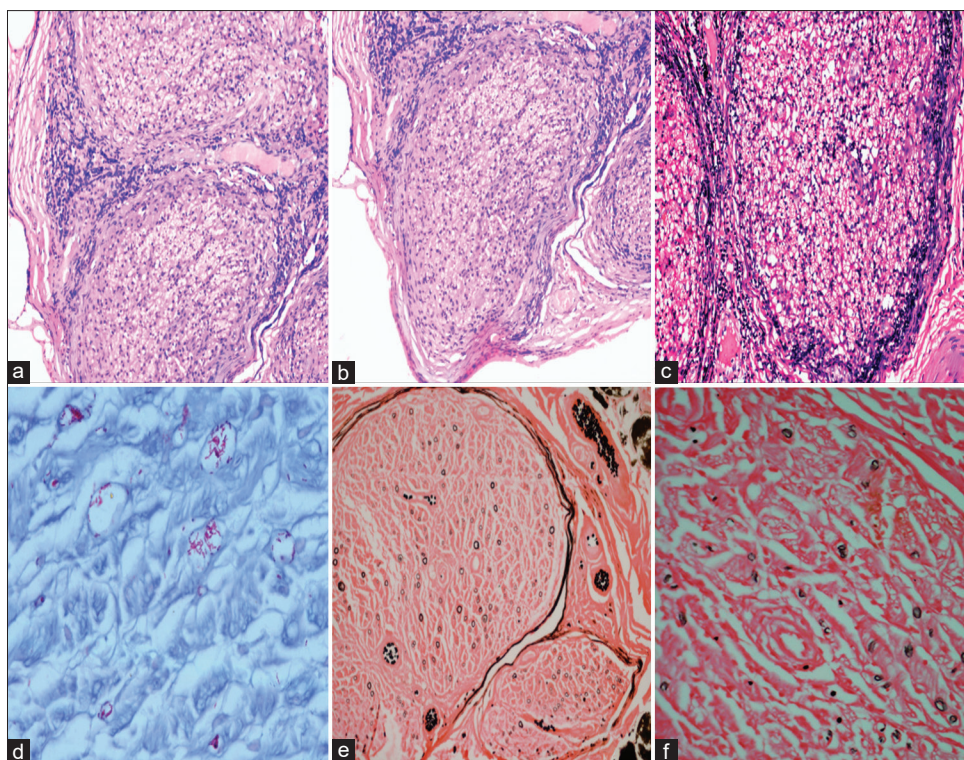


Figure 1: (a, b and c) Expanded fascicle with foamy histiocytes in the endoneurium and inflammatory infiltrate extending to perineurium and epineurium, H and E X40 (a), X100 (b), and X400 (c); (d) Globi of lepra bacilli within the macrophages, 5% Zeihl Nelson stain X400 (e and f) Nonuniform involvement of the fascicles with thinly myelinated nerve fibers, Kpal X100(e) and X400(F)

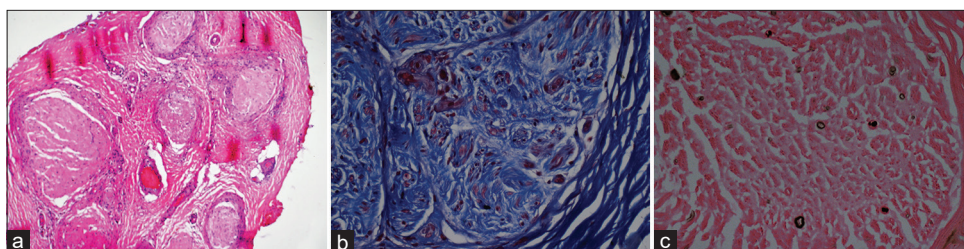


Figure 2: (a and b) Perineurial thickening with marked endoneurial fibrosis and microfasciculations, H and E X40 (a) and Masson Trichrome X400(b); (c) thinly myelinated nerve fibers, Kpal X400

of leprosy neuropathies dominantly show axonal depletion and myelin stains demonstrate almost complete depletion of myelinated nerve fibers. The electrophysiology studies have revealed segmental demyelination while others have reported axonal polyneuropathy.^[1,2] The axonal pattern vs demyelination can also be differentiated on nerve biopsy where the presence of thin myelin rings is a piece of evidence for demyelination. In this article, we have tried to concentrate on the nerve biopsies of leprosy neuropathy wherein we identified dominant demyelinating changes on myelin stains. These changes were observed in a limited number of biopsies which we are attempting to elaborate below. The details of seven such cases are provided:

Of the 86 patients of leprosy neuropathy diagnosed over a period of 3 years, seven patients (8.1%) had a demyelinating pattern of neuropathy. The age of the patients ranged from

25 to 48 years. There was no history of diabetes in any of the patients and the viral markers were negative. All the patients presented with sensory symptoms such as paresthesia, tingling numbness, and burning sensation predominantly involving the lower limbs, foot, and toe. There were no motor deficits in any of the patients except one who had weakness of both legs. The deep tendon reflex was preserved in all the patients. The duration of the symptoms ranged from 1 month to 3 years. Nerve conduction studies revealed sensory axonal neuropathy in five patients and one patient each of demyelinating sensory neuropathy and symmetrical sensory neuropathy. Conduction blocks were reported in two patients. Three patients were already diagnosed with leprosy prior to the onset of neuropathy. Two of them were diagnosed 2.5 and 3 years back and completed treatment while another patient was still on treatment when he developed the symptoms of neuropathy.

Table 1: Clinical and histopathological features of all leprosy neuropathy patients

No of cases	Nerve conduction studies	Prior treatment history	Histopathology	Endoneurial fibrosis	Acid-fast bacilli	Treatment/follow-up
Case 1	Sensory axonal neuropathy	Developed symptoms of neuropathy during the course of the treatment	Lepromatous leprosy	Not present	Positive	No complaints after completion of treatment
Case 2	Asymmetrical demyelinating sensory neuropathy	Nil	Lepromatous leprosy	Not present	Positive	Lost to follow up
Case 3	Sensory axonal neuropathy	Completed treatment 2.5 years back	Extensive fibrosis	Marked	Negative	Symptoms persisting after treatment
Case 4	Sensory axonal neuropathy	Completed treatment 3 years back	Extensive fibrosis	Marked	Negative	No complaints after completion of treatment
Case 5	Symmetrical sensory neuropathy	Nil	Lepromatous leprosy	Mild to moderate	Positive	On treatment and symptoms persisting
Case 6	Asymmetrical sensory-motor axonal neuropathy	Nil	Borderline lepromatous leprosy	Not present	Positive	Discontinued treatment
Case 7	Sensory axonal neuropathy	Nil	Tuberculoid leprosy	Not present	Negative	On treatment

Biopsies were classified as per Ridley–Jopling classification and showed characteristic features of lepromatous leprosy (LL) leprosy in three patients and one each tuberculoid and BL leprosy. There were two patients who were on prior treatment with multidrug therapy showed dense fibrosis with classic microfasciculations without any evidence of active disease. All the biopsies showed perineurial thickening. Foam cells were seen in the endoneurium in four biopsies. One biopsy showed endoneurial granulomas. However, necrosis or multinucleate giant cells were not seen. Lepra bacilli were seen on the special stain with Fite Faraco in four biopsies, of which classic “globi” were identified in three biopsies. Kulchitsky pal (Kpal) stain highlighted thinly myelinated nerve fibers indicating de/re-myelination. The histopathological features are depicted in Figures 1 and 2. Associated axonal loss in the form of endoneurial fibrosis was observed in three biopsies. The axonal loss was characterized by immunohistochemistry with neurofilament stain. The biopsies did not show any onion bulbs and myelin ovoids ruling out other inflammatory demyelinating neuropathy. The clinical and histopathological features of all the patients are summarized in Table 1.

On follow-up, two patients responded well to treatment and are asymptomatic following the completion of treatment. The symptoms persisted in two patients and one patient discontinued treatment. One patient was started on treatment and another patient was lost to follow-up.

The nerves are damaged and destroyed at any time during the course of the disease in leprosy.^[3] There have been few studies characterizing the nerve biopsy pathology in pure neuritic leprosy (PNL).^[4-6] Axonal loss has been found to be the most consistent feature in leprosy nerve biopsies. We have studied and reported earlier that endoneurial inflammation, dense fibrosis, and reduction in the number of myelinated nerve fibers are strong supportive indicators of PNL regardless of acid-fast bacilli (AFB) positivity. Other studies also support these findings.^[6,7] The classic microfasciculations seen in the

endoneurium also result due to endoneurial fibrosis. However, there are few studies that characterize demyelination in nerve biopsy in patients of leprosy neuropathy.^[8] Electrophysiologic evidence of demyelination in leprosy neuropathy has been definitely established and reported.^[9]

The presence of significant endoneurial fibrosis indicates collagen deposition in the endoneurium resulting in axonal degeneration. Three biopsies in the present study showed significant fibrosis indicating demyelination secondary to axonopathy. The destruction of the nerve fibers by the inflammatory process in tuberculoid leprosy leads to axonal loss. Axonal damage interferes with the transfer of signal along the axon Schwann cell pathway leading to demyelination.^[10]

The early stage of nerve damage initiated by contact of the bacilli to Schwann cells elicits no inflammation and biopsy reveal subperineurial edema, axonal atrophy and demyelination. The second phase is mediated by lymphocytes and macrophages and encompasses tuberculoid and LL. The presence of autoantibodies to various components of the nerve has been regarded as the underlying mechanism of demyelination in the later phase of nerve damage.^[11]

Direct Schwann cell toxicity by lepra bacilli has also been thought to be pathogenesis in demyelination.^[12] The non-immune mechanism including the release of interleukins and complement activation has also been attributed to leprosy demyelination. These are seen in patients with type 2 lepra reactions. Three of the patients in our study were on treatment for cutaneous leprosy. The nerve involvement and demyelination in these three patients could perhaps be attributed to lepra reactions initiating demyelination.

Demonstration of demyelination requires examination of teased fibers and electron microscopy. However, teased fiber studies are extremely laborious and time-consuming even with technical expertise. The presence of thin myelin rings on

biopsy is a good indicator of de/remyelination. Special stains for collagen and myelin along with neurofilament is a reliable way of distinguishing primary from secondary demyelination. The presence of inflammation and demyelination also brings in a differential of CIDP. The Fite Faraco staining definitely helped in the diagnosis of leprosy in these patients since the classic granulomas and necrosis were absent. This highlights the importance of nerve biopsy analysis in leprosy neuropathy with special reference to the demyelinating pattern. Leprosy should be considered as an important and treatable cause of demyelinating neuropathy and stains for lepra bacilli should be a routine part of nerve biopsy analysis for diagnosis of infectious inflammatory neuropathies especially in endemic countries like India.

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Conflicts of interest

There are no conflicts of interest.

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