Lepromatous Leprosy and associated proprioceptive loss

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Abstract:
Background: Leprosy presents commonly with mononeuritis multiplex, affecting mainly the exteroceptive sensations. Neuropathy with a significant afferent large fiber element is considered to be an uncommon manifestation of leprous neuropathy. Aims: To evaluate the clinical and neurophysiologic aspects of a sub set of patients with leprous neuropathy having clinical proprioceptive loss.

Settings and Design: Prospective study of patients with a diagnosis of peripheral neuropathy secondary to leprosy having proprioceptive loss.

Materials and Methods: Consecutive patients seen during a 2 year period (2004 and 2005) diagnosed to have leprous neuropathy with proprioceptive abnormalities on clinical examination were included. The diagnosis of leprosy was achieved by positive skin biopsy, split skin smears or nerve biopsy. Their clinical and electrophysiologic characteristics were studied. Statistical methods: The results were analyzed using various tests of significance, including Pearson Chi-Square test. Values less than 0.05 were considered to be statistically significant.

Results and Conclusions: We observed predominance (78.95%) of multibacillary forms of leprosy. Symmetrical neuropathies outnumbered mononeuritis multiplex (12:7). The pan sensory neuropathy had a mean duration of 24.32 months, but sometimes appeared early in the course of the disease. Areflexia and electrophysiologic evidence of proximal affection was common, reflecting proximal spread of neuropathic process. Such patients have higher incidence of developing deformities and ulcerations and they represent a vulnerable sub set of patients with leprosy.

Key words: Leprosy, proprioception, electrophysiology, multibacillary, mononeuritis multiplex, polyneuropathy.

I. Introduction:
Leprosy is a chronic infectious disease of the skin, peripheral nerves and other tissues, resulting from interplay of immune responses of host to Mycobacterium leprae. It was believed that leprosy predominantly involved the skin with affection of the cutaneous nerves. With better understanding of the disease, pure neuritic forms of leprosy are increasingly being recognized. The affection of nerves is known to take various forms. The disease is known to preferentially involve only the exteroceptive sensations but proprioceptive sensory loss has been described rarely in subjects with leprosy 1. We undertook the present study to evaluate the clinical and neurophysiologic aspects of a sub set of patients with leprous neuropathy having proprioceptive abnormalities on clinical examination.

II. Material and methods:
Consecutive patients with a diagnosis of peripheral neuropathy secondary to leprosy having proprioceptive loss seen over the period of two years [2004 and 2005] from a tertiary referral center were studied. The diagnosis of leprosy was based on specific histopathological abnormalities either on a nerve or skin biopsy or a slit skin smear examination. The patients were classified using Ridley and Jopling classification 2. All patients underwent the following steps of evaluation: A detailed history and neurological examination was done. Type I lepra reaction was diagnosed when there was development of acute erythema and swelling of existing skin lesions with appearance of new ones, acute nerve pain, tenderness with fresh or worsening, Kural impairment with edema of hands and feet. Type II lepra reaction was identified by the presence of 40 temic symptoms including fever, malaise, recurrent transient cutaneous nodules, acute/ sub acute nerve enlargement, and tenderness and in severe cases arthritis, uveitis and orchitis 3. Laboratory investigations [ESR, CBC, HIV, Blood sugar, liver and kidney function tests] were done in all patients and ANA, ANCA and anti ds DNA were performed when feasible. All patients underwent a detailed electromyography and nerve conduction study. Nerve conduction velocity (NCV) studies and electromyography (EMG) were done using standard techniques 4. Multiple motor nerves, i.e. median, ulnar, radial, peroneal and tibial nerves were measured bilaterally in all individuals and anti dromic sensory nerve conduction studies were performed on the median, ulnar, superficial radial, superficial peroneal and sural nerves bilaterally. Semi quantitative EMG was performed with concentric bipolar needle electrodes on various muscles of the upper and lower limbs, including the proximal muscles like...
the biceps and deltoid in the upper limbs and quadriceps (vastus medialis) in the lower limbs. Statistical analysis: The results were analyzed using various tests of significance, including Pearson Chi-Square test. P values less than 0.05 were considered to be statistically significant.

III. Results

Preliminary data: Nineteen patients fulfilled the inclusion criteria. Males (84.21%) outnumbered females; the mean age of presentation was 44.05 years in our subjects. Using the Ridley-Jopling classification; the present study included 4(21.05%) patients with LL (lepromatous leprosy), 9(47.37%) patients with BL (Borderline lepromatous leprosy), 3 (15.79%) patients with TT (Tuberculoid leprosy) and 1 (5.26%) patient with BT (borderline tuberculoid leprosy). There were 2(10.53%) patients with PNL (pure neuritic leprosy) (all with more than 1 nerve involvement). Using the WHO classification, we observed 4 (21.05%) patients of PB (paucibacillary) group and 15(78.95%) of MB (multibacillary) group. The mean duration of symptoms in our subjects was 24.32 months (range 1 to 108 months).

Clinical features:

History: Most of our subjects complained of numbness [18 (94.74%)]. 16(84.21%) subjects complained of weakness; paraesthesia and skin lesions were complained by in 13(68.42%) and 12(63.16%) patients each. Deformities (5 in those with pan sensory loss and 1 with mononeuritis multiplex) and ulcers were present in 6(31.58%) and 5(26.32%) of our subjects respectively. Five patients (26.32%) had ulcer as the presenting symptom. Of these; 4 patients belonged to lepromatous group (3 patients with LL & 1 patient with BL), whereas the fifth patient had tuberculoid leprosy (TT). Patients with deformity had higher duration of symptoms (48 to 108 months) as compared to those without it (18.77 months) (p 0.185 not significant). Our patients had a very wide duration of symptoms, 1 to 108 months.

Examination: 94.74% of patients had thickened nerves and 89.47% had hypoesthetic skin patches. Exteroceptive and proprioceptive sensory loss was present in all the patients. 12 patients had symmetrical neuropathies and the remaining 7 had mononeuritis multiplex. Weakness on examination was present in 16 (84.21%) of the patients. Regional areflexia [loss of deep tendon reflex in the distribution of the affected nerve] was observed in 12 (63.16%) patients. The mean duration of symptoms in these patients with regional areflexia (31.67 months) was higher than those with retained reflexes (11.71 months) (p 0.114 not significant). Regional areflexia was observed more often in subjects with lepromatous leprosy (BL-50%, LL- 64.7%) and PNL (100%).

Investigations: The mean hemoglobin level in our subjects was 12.3 gm/dl. Mean ESR was 25.84 mm at end of 1st hour (4 to 90 mm). ANA, dsDNA & ANCA levels were done in 5 patients; it was negative in all. One patient was seropositive with an ESR of 90 mm at the end of 1 hour. Electrophysiology: The nerves commonly affected on motor nerve conduction studies (NCS) were peroneal (84.21%), posterior tibial (78.95%) and ulnar nerves (68.42%). 47.37% of median nerves and only 21.05% of radial nerves were affected on motor NCS. Abnormality of motor studies correlated (especially F waves) with presence of weakness clinically (p = 0.001 significant). The most commonly affected nerve on sensory nerve conduction study (SNC) was the ulnar (100%) nerve followed by the superficial radial (94.74%) nerve. The superficial peroneal and sural nerves were abnormal in 89.47% of patients each. The median sensory nerve abnormalities were seen in 78.95% of the patients. 68.42% of the patients had nerve conduction findings suggesting of an axonal neuropathy. Demyelinating and mixed (axonal and demyelinating) neuropathies were seen in 15.79% of our subjects each.

F and H responses: F wave abnormalities were observed in 89.47% and H reflex abnormalities in 63.16% of the patients. H reflex abnormalities were observed more frequently in those subjects with longer disease symptoms. Mean duration Of symptoms in patients with H reflex abnormality was 30.83 months, as against in those with normal H reflex wherein the mean duration of symptoms was 13.14 months.

Electromyographic abnormalities were most commonly seen in the distribution of the peroneal and ulnar (84.21% each) nerves. The other nerves were affected in the following order; posterior tibial (78.95%), median (57.89%) and radial (36.84%) nerves. EMG abnormalities were associated with motor weakness on examination

Pathology: Slit skin smear examination (SSS): All the patients underwent a slit skin smear examination and 13 patients were diagnosed as leprosy based on acid fast bacillus positivity. Of these 9 had BL and 4 had LL. Skin Biopsy: Skin biopsy was performed and was positive in 1 patient who had borderline lepromatous leprosy. Nerve biopsy: Nerve biopsy was obtained in 7 patients and showed evidence of leprosy in 6 patients. The biopsy was normal in 1 patient (14.29%). This patient had positive skin pathology.
IV. Discussion:

Preliminary Data: The mean age of presentation [44.05 years] and the male predominance 5 [84.21%] seen in the present study match with most studies 3, except those in some areas of Africa, where females are more commonly affected 4. The mean duration of symptoms in our patients was long, being 24.32 months and the prevalence of various types of leprosy seen in the present study is in accordance with published data 6.

Clinical Features of Neuropathies:

On clinical evaluation, symmetrical neuropathies outnumbered mononeuritis multiplex [12/7]. The patients with symmetrical neuropathies belonged to the lepromatous group which is in accordance to published literature; those with severe and wide spread involvement have a glove and stocking pattern of sensory loss 3. These patients had higher association of deformities and ulcers and SSS was positive in most of them (11/12). 2 patients were in reaction states. As against this, the group with the mononeuritis multiplex pattern had fewer deformities, the SSS was less often positive (2/7) and none of these patients were in reaction states.

Studying all 19 patients as a whole, it was seen that these patients with proprioceptive loss tended to be in multibacillary category [78.95%], suggesting that increased bacillary load results in pan sensory affection of the peripheral nervous system. The proprioceptive loss related strongly with the development of ulcers and deformities. Simultaneously studied patients of lepromatous neuropathy [n= 31; not included in the present study] who did not have proprioceptive a loss did not have ulcers and deformities except in one of them. Patients with proprioceptive loss have increased chances of complications related to the increased presence of deformities; a having a bearing on the management of such patients.

Proprioceptive loss has been reported only occasionally in lepromatous neuropathy. Van Barkel et al found joint position sense abnormalities in only 7 of 303 multibacillary patients with lepromatous neuropathy 7. Pandya et al 8 reported six such patients who presented with progressive sensory ataxia and had pseudo-athetosis of fingers and generalized areflexia. In one of their 4 patients, histopathology of lumbar sensory ganglion revealed extensive neuron loss and degeneration with reactive proliferation of capsular cells; an inflammatory focus of lymphocytes. No bacilli were detected in the specimen. Authors suggested that proprioceptive loss in those patients was as a result of 'leprous ganglionitis'. Misra et al 9 have reported a single patient with a a a BTH in type 1 reaction, who clinically had pseudo-athetosis. One patient in the present study was demonstrated to have not only ganglionitis, but more proximal involvement in form of a spinal cord granuloma on Gadolinium enhanced MRI scan of cervical spine. [Figure 1] His electrophysiological studies demonstrated proximal involvement. [Neurology India: in press: Oct • 2007] Studying the proprioceptive loss in time frame, it was clear that even though the mean duration of the group was long; the range was very wide; being 1 to 108 months. The proprioceptive sensory loss did not have significant relation to duration of symptoms. This finding is intriguing as severity of neuropathy logically would increase with the duration of disease. Immune factors of host parasite reaction may be relevant in the development of the pattern of neuropathy. It is tempting to postulate that lepra reactions may have been responsible for the severe nerve damage. Even though evidence of lepra reactions was present in only 2 patients, burnt out reactions in the past may have eluded documentation but be responsible. This aspect needs further exploration, as immunosuppressive therapy at an early stage may become important in preventing the immune related nerve damage and its sequel. Weakness and regional areflexia: In the present study, 16 (84.21%) patients had weakness on examination, pointing to affection of large myelinated nerve fibers going hand in hand with the proprioceptive loss. In the present study we observed regional areflexia in 63.16% of the patients. These patients had a longer duration of symptoms as compared to those without areflexia [31.67 months v/s 11.71 months] which has been previously noted9. The areflexia has been believed to suggest proximal extension of the neuropathy and seen more often with reaction states 5. In the present study, 2 patients were in reaction state and one of them had areflexia.

Electro diagnosis: The sensory and motor nerve conduction studies showed abnormalities suggesting axonal neuropathy. We had 3 subjects with a predominant demyelinating neuropathy; and in one of them, the duration of illness was long, being 108 months. This patient is unusual as demyelinating neuropathies are seen early in the disease process. 10

F wave and H reflex study: F wave and H reflex abnormalities were common in our patients. In view of the distal segment involvement evidenced by reduced CMAP and SNAPs; the interpretation of abnormalities in F and H reflex is speculative but may suggest additional proximal affection of the neural pathway in patients of leprosy having proprioceptive loss. H reflex abnormalities were associated with a higher mean duration of symptoms [30.83 months; as against in those with normal H reflex wherein the mean duration of symptoms was 13.14 months].

Electromyography: EMG showed evidence of denervation in the distribution of 116 nerves, as compared to abnormalities of motor NCS in 96 nerves suggesting that EMG is more sensitive in diagnosing motor affection in leprosy.
Nerve biopsy: Histopathological examination of a cutaneous nerve is required to diagnose primary neuritic leprosy. It could also be obtained in cutaneous nerves under the skin patch, if skin biopsy or smear is negative. Pannikar et al. 12 studied radial cutaneous nerve biopsy in patients of leprosy and found negative results in 35% of patients. In present study, nerve biopsy was obtained in 7 patients and showed evidence of Hansen’s disease in 6 patients. The biopsy was normal in 1 patient (14.29%). The incidence of negative results on nerve biopsy was less as compared to that found by Pannikar et al. 11 It could be related to patchy nature of the infectious process.

V. Conclusions:

This small series studies the clinical and electrophysiological characterization of subjects with leprous neuropathy having proprioceptive sensory loss. These patients appear to form a distinct sub type of leprous neuropathy. Such patients have multibacillary forms of leprosy; develop a pan sensory neuropathy, being often symmetrical and sometimes early in the course of the disease. Areflexia and electrophysiological evidence of proximal affectation is common, reflecting proximal spread of neuropathic process. The extent and the severity of the process do not seem to link to the duration of disease; but to an extent, correlate with the bacterial load. It is speculated that these changes relate to the immune factors of the host parasite reaction and needs further evaluation. As these patients have higher chances of developing deformities and ulcerations, they represent a vulnerable sub set of patients with leprosy.

References: