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Original Article

A Clinicopathological Study of Pure Neuritic Leprosy

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The clinical diagnosis of pure neuritic leprosy (PNL) can be made by the presence of definite nerve enlargement with sensory impairment along the supply of that nerve. But a diagnosis based only on clinical findings should be made with great care because rarely other diseases can cause palpable nerve thickening with/without regional anaesthesia. Therefore, sometimes, histopathological evidence is necessary to establish the correct and definitive diagnosis. Aim of this study was to analyse the histopathology of sural nerve and anaesthetic skin in PNL and to study its clinical pattern. PNL patients were clinically diagnosed and assessed. Sural nerve biopsy was done from the side of the clinical involvement. Skin biopsy was done from the area having maximum sensory impairment. Clinical and histopathological data were analysed. Twenty-five patients were diagnosed and analysed who attended the OPD between September 2001 to February 2003. Sural nerve biopsy was suggestive of leprosy in 13(52%) patients. Among these histopathology suggestive cases, the most common histological picture was of Indeterminate (Ind) type. Skin biopsy from anaesthetic area showed features of leprosy in 10(40%) patients. Sensitivity of combined sural nerve and skin biopsy in diagnosing PNL was 68%. Sural nerve biopsy can be used as a diagnostic aid in PNL if there is involvement of lower limb even if sural nerve is not clinically involved. This can be combined with biopsy from anaesthetic skin so that more number of leprosy cases may be confirmed histopathologically.

Keywords : pure neuritic leprosy, sural nerve biopsy, anaesthetic skin biopsy

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Introduction

Leprosy is a chronic mycobacterial, granulomatous disease caused by *Mycobacterium leprae*, affecting the peripheral nervous system, the skin and certain other tissues. The concept of a sub type of leprosy with enlargement of one or more nerves but no discernible skin lesions is now well established and accepted, especially in India. Wade (1952) was the first to recognize pure neuritic as a separate sub type in the classification of leprosy. Indian Association of Leprologists (IAL) has recognized Pure Neuritic Leprosy as a distinct group (IAL 1955, 1982). Pure Neuritic leprosy (PNL), presents with signs and symptoms of nerve deficit, which may be sensory with or without motor involvement and without any visible skin patch/lesion. The clinical diagnosis can be made by the presence of definite nerve enlargement with sensory impairment along the supply of that nerve (WHO 1988). But the diagnosis of PNL based only on clinical findings should be made with great care. Diseases like amyloidosis of peripheral nerves and certain types of hereditary sensory-motor neuropathies can also present with palpable nerve thickening with regional anaesthesia (Jopling, Mc Dougall 1995). PNL type of leprosy is skin smear negative for AFB, however, secondary neuritic leprosy (nerve thickening is present, but the skin lesions may have regressed and not visible), may be skin smear positive for AFB. Therefore, histopathological evidence is sometimes necessary especially in non endemic settings, to establish the diagnosis of leprosy and institute specific treatment.

Neurotropism is a unique feature of *Mycobacterium leprae*. It is the only bacterium/infectious agent known to infect peripheral nerves which leads to Schwann cell disintegration and peripheral nerve infiltration (Antia 1982). Thus nerve biopsy is an important tool which helps in the correct diagnosis and classification of the disease. Few other studies have also suggested that there is histological evidence of involvement of the skin in PNL and that skin biopsy from the affected neural compartment is helpful in the definitive diagnosis of the disease (Suneetha et al 1998).

As disease profiles are dynamic, may change with evolution of population and pathogen as well as with changing therapy and its access, studies on disease characteristic at different time periods remain important. This study was conducted to understand the clinical pattern of PNL, to determine the role of sural nerve biopsy in the diagnosis of PNL and to classify the histopathological changes if present in the nerve and to determine the role of skin biopsy from the area of impaired sensation as a diagnostic aid in PNL.

Patients and Methods

After obtaining ethical clearance from Institutional Ethical Committee, an observational, descriptive study was conducted for a period of one and a half year year from 1st September, 2001 to 28th February 2003 on newly diagnosed PNL patients attending the Department of Dermatology, Venereology and Leprosy of Government Medical College, Thiruvananthapuram, Kerala, which is a tertiary care centre A diagnosis of PNL was made in patients with signs and symptoms of nerve deficit along with thickened peripheral nerves and absence of any skin involvement (IAL 1982). After obtaining informed consent, predesigned proforma was filled, maintaining the confidentiality. A detailed history was taken and a thorough general, dermatological and systemic clinical examination was carried out in each patient and documented. Detailed examination of peripheral nerves for thickening, tenderness, sensory and motor deficits were done and recorded.

Slit skin smears from the ear lobes for acid fast bacilli detection after ZN staining were done in all

patients. The clinical features were taken as the gold standard and based on this the diagnosis of PNL was made in all the examined cases. Biopsies were taken from the skin with impaired sensation and from the sural nerve of the same side of involvement. The site for nerve biopsy was selected based on sural nerve involvement in the form of thickening or showed features of peripheral nerve deficit in the supply area. In few patients who had only upper limb involvement, sural nerve biopsy was done from any one side. The technique of sural nerve biopsy described by Dyck et al (1968) was followed in this study except that the fascicular biopsy as described by the authors was replaced by full section biopsy (Theriault et al 1998) of nerve as it is known that leprosy disease may not involve all the fascicles. The incision was carried at about 8 cm proximal to lateral malleolus and just lateral to Achilles tendon. The nerve was clamped by two artery forceps and the nerve in between was cut and sent for histopathological examination. The cut ends of the nerve were approximated and sutured with 4-0 proline. Skin biopsy was taken by either 4 mm punch or elliptical biopsy from the area having maximum sensory impairment. Skin biopsy included full depth of dermis together with a portion of subcutaneous fat. Biopsy specimens were stained with Haematoxylin and Eosin and with Fite-Faraco stain. Histopathological changes in the nerve and skin were studied in terms of type, location, pattern and amount of infiltrate and presence of acid fast bacilli (AFB). Histo-pathological classification by Ridley and Jopling was done with skin biopsy. In the nerve, a histological diagnosis of Indeterminate leprosy was made when nerve showed lymphocytic infiltrate with or without AFB; diagnosis of Tuberculoid leprosy was made when infiltrate of epithelioid cells with or without Langhan's giant cells and lymphocytes were seen with or without AFB; Borderline leprosy diagnosis was made, when in addition to the above infiltrate some macrophages and few foam cells were present, with AFB; and diagnosis of Lepromatous leprosy was made when plenty of macrophages filled with acid fast bacilli were observed (Kaur et al 1991). Statistical analysis was done using descriptive statistical method. Sensitivity analysis of sural nerve biopsy and skin biopsy were also done.

Results

Twenty five patients with PNL were diagnosed during the above period, The youngest age observed in the group was of 19 years and the oldest patient was of 67 years. The mean age was 41.8 years with maximum belonging to 41 - 60 years age group. Genderwise there were 22 males and three females. Seven patients (28%) were manual workers by profession. The duration of symptoms present before reporting to the facility varied from 3 weeks to 8 years. Majority of patients i.e. - 15 patients (60%) had a duration of symptoms for more than 1 year. Sensory symptoms were the presenting complaint in 13(52%) patients; sensory and motor symptoms in 12(48%) patients, while no one presented with motor symptoms alone. Two patients also presented with nerve abscess. Visible deformities were present in the form of plantar ulcers in three patients, foot drop in three and ulnar clawing in

Table 1 : Thickened Peripheral nerves in the series

Thickened nerve	Number of patients
Common peroneal nerve	21(84%)
Ulnar nerve	16(64%)
Posterior tibial nerve	12(48%)
Superficial peroneal nerve	12(48%)
Sural nerve	12(48%)
Radial cutaneous nerve	7(28%)

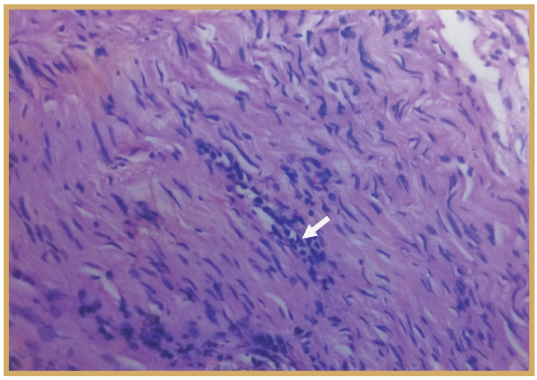

Fig 1 : Nerve showing mononuclear cell infiltrate, consistent with - Hansen's disease – indeterminate (x100, H & E stain)

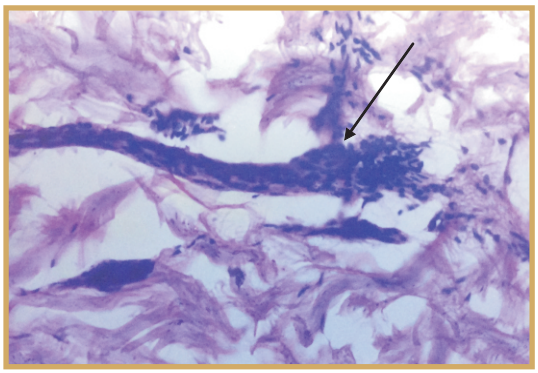

Fig 2 : High power view of skin showing hypertrophied nerve with perineural infiltrate, consistent with Hansen's disease – indeterminate (x 100, H & E)

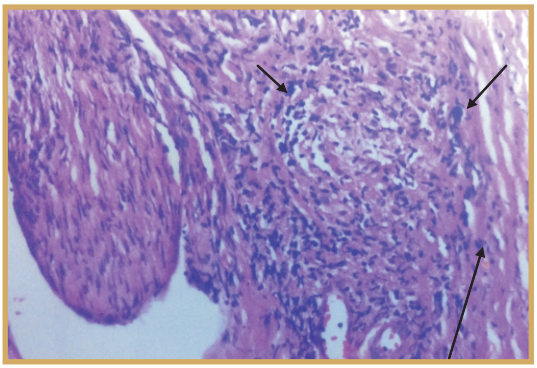

Fig 3 : High power view of nerve showing epithelioid cell granuloma, consistent with Hansen's disease - tuberculoid (x100, H & E)

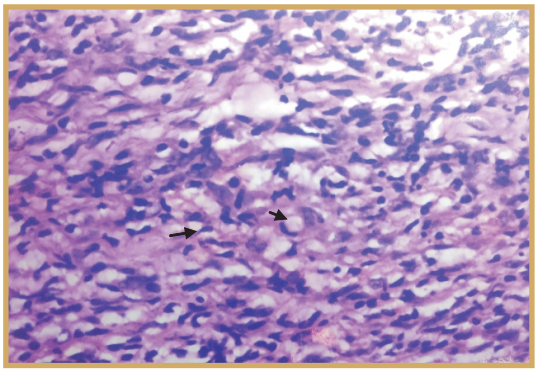

Fig 4 : High power view of nerve showing mononuclear cells and foam cells, consistent with Hansen's disease - borderline (x100, H & E).

Table 2 : Sural nerve biopsy findings in PNL cases investigated in present study

Histopathological features	Number of patients
Diagnostic changes of leprosy	13(52%)
Histological Diagnosis of Indeterminate leprosy	6(24%)
Histological Diagnosis of Tuberculoid leprosy	5(20%)
Histological Diagnosis of Borderline leprosy	2(8%)
Histological Diagnosis of Lepromatous leprosy	0(nil)
Total	25(100%)

one patient. Upper limb alone was involved in three patients, lower limb alone in 10 patients and both upper and lower limb involvement in 12 patients. Two patients gave history of multibacillary leprosy contacts in the family.

On examination, none of the patients had skin lesions suggestive of leprosy. Peripheral nerve thickening was present in all patients. Most commonly involved thickened nerve in the series was the Common Peroneal nerve. Single nerve was involved in seven patients, while in the rest of

Table 3 : Correlation between nerve thickening and histopathological involvement of sural nerve

Sural nerve clinically	Sural nerve histologically affected	Sural nerve-not histologically affected	Total
Thickened	8	4	12
Not thickened	5	8	13
Total	13	12	25

Table 4 : Evidence of Histopathological involvement of sural nerve in relation to the site of involvement in present series

Site of involvement	Sural nerve histologically affected	Sural nerve not histologically affected	Total
Upper limb alone	0	3	3
Lower limb and upper limb involvement	13	9	22

Table 5 : Table showing skin biopsy findings

Histopathological features	Number of patients
Diagnostic of leprosy	10(40%)
Indeterminate Leprosy	8(32%)
BT leprosy	1(4%)
BL leprosy	1(4%)
Nonspecific inflammatory infiltrate	6(24%)
Normal skin	9(36%)

Table 6 : Analysis of diagnostic efficacy of sural nerve biopsy and anaesthetic skin biopsy

Histopathological findings suggestive of leprosy	Number of patients	Percentage %
In skin only	4	16
In nerve only	7	28
In skin and nerve	6	24
Total	17	68

18 patients, multiple nerves were thickened. (Table 1) Ear lobe slit skin smear were negative for AFB in all the 25 patients. On histopathological examination of sural nerve, diagnostic changes of leprosy were present in 13 out of 25 patients. Changes in sural nerve were classified as reported by Kaur et al (1991) and shown in table 2. Histologically 6 were consistent with indeterminate (Figs 1 and 2); in 5 it was consistent with Tuberculoid leprosy (Fig 3): in 2 with Borderline leprosy (Fig 4). Sensitivity of sural nerve biopsy in diagnosing leprosy was 52%.

Correlation between nerve thickening and histopathological involvement of sural nerve is shown in Table 3. Sensitivity of sural nerve biopsy in diagnosing leprosy from clinically thickened sural nerve was 66.67% (8/12). Sensitivity of sural nerve biopsy in diagnosing leprosy from sural nerve which was not thickened was 38.46% (5/13). Sensitivity of sural nerve biopsy in diagnosing leprosy if lower limb was not involved was 0%. Sensitivity of sural nerve biopsy in diagnosing leprosy if lower limb was involved was 59.1%. (Table 4)

Biopsy from anaesthetic skin area showed changes diagnostic of leprosy in 10 patients (Table 5) so that sensitivity of anaesthetic skin biopsy was 40%. Most frequently observed findings in

such cases was of Indeterminate leprosy (8/25; Fig 2). Further out of 25 patients, 17/25 (68%) could be histopathologically confirmed as leprosy either by nerve or skin biopsy (Table 6).

Discussion

PNL as, included in Indian classification, forms about 4 to 18 % of the total new leprosy patients detected in India (Sharma and Malhotra 2008, Mendiratta et al 2006, Noordeen 1972). The mean age of patients diagnosed as PNL was 37.19 years as reported by Kaur et al (1991) while in the present study, 22 out of 25 PNL patients, belonged to 21-60 years age group. The same authors had observed a male preponderance as observed in the present study (male to female ratio was 22:3). PNL patients usually give history of long duration of symptoms before presentation (Uplekar and Antia 1986) which can be explained due to absence of visible skin lesions and only impairment of sensations. In our study too, majority (60%) were diagnosed after one year of development of symptoms. PNL presents clinically as peripheral neuropathy with functional impairment of single or multiple nerves, but without two of the cardinal signs of leprosy i.e., the typical skin lesions and the presence of acid fast bacilli. Predominant symptom is sensory impairment. Some patients may present with both sensory and motor symptoms but none of the studies reported patients with purely motor symptoms (Rao and Suneetha 2016). In the present study, 13(52%) patients presented with sensory symptoms and 12(48%) patients presented with both sensory and motor deficits.

Usually several nerves are involved in PNL. Single nerve involvement was seen in 7 patients in this study, while the rest of them (18/25) had multiple nerve involvement. In a large study on PNL from India, (Kumar et al 2004) it was noted that out of 65 patients, 26 (40%) were mononeuritic while in 39 (60%) of cases more than one nerve trunk was involved, either on the same limb or on different limbs. Involvement of upper extremities and ulnar nerve was the most common clinical feature in earlier studies (Rao and Suneetha 2016, Kumar et al 2004), however, in the present study, lower limb was more commonly involved, and the most commonly involved nerve observed was the common peroneal nerve. Nerve trunks such as ulnar, common peroneal and posterior tibial nerves which provide sensation to hands and feet, are commonly observed to be involved in PNL. This leads to WHO Grade 1 disability, in most cases of pure neuritic leprosy. Progression to Grade 2 disability is also common, unless recognized, diagnosed and managed promptly. Disabilities observed at the time of presentation were seen in 48% (Mahajan et al 1996) and 50% (Mendiratta et al 2006) of PNL patients in studies conducted in Pune and New Delhi respectively. In this series 12/25 patients (48%) presented with Grade 2 disabilities at the time of diagnosis of the disease.

All the patients were skin smear negative for AFB. Treatment in PNL is based upon the number of nerves involved. According to present NLEP guidelines in India, if single nerve is involved in PNL it is considered as paucibacillary and treated accordingly, and when more than one nerve is involved, it is considered as multibacillary for therapeutic purposes (MoHFW, GoI 2013).

The diagnosis of PNL and its differentiation from other causes of peripheral neuropathy may be difficult at times (Jopling and McDougall 1995). In regions endemic for leprosy, there is a tendency to attribute PNL as a cause of peripheral neuropathy without adequate investigations. Investigations such as nerve conduction study may show sensory motor deficits suggestive but not diagnostic of leprosy (Ramadan et al 2001). Cutaneous nerve biopsy is a simple office procedure which does not require any sophis-

ticated equipment and has been found to be useful in diagnosis of peripheral neuropathy. Few side effects may occur with this procedure (Theriault et al 1998). Minor wound infection, wound dehiscence and stump neuromas can occur. Approximately one third of the patients particularly those without much sensory impairment at the area of innervation of sural nerve report unpleasant symptoms at the biopsy site. The area of original sensory deficit declines by 95% after 8 months by collateral innervations (Theriault et al 1998). It was found that the sequelae like dysaesthesia and persistent pain regress and finally subside over time.

Histopathological changes in sural nerve suggestive of leprosy were found in 13 patients, i.e 52% of present study. In the study conducted by Jacob and Mathai (1988), 38 out of 77 patients (49.4%) of peripheral neuropathy patients showed features of leprosy on nerve biopsy. The entire leprosy spectra were observed in the nerve biopsies except lepromatous leprosy. Pure lepromatous histology was not observed in any of the patients which is similar to other studies (Rao and Sunetha 2016). Only few studies (Kaur et al 1991, Jacob and Mathai 1988) have reported pure lepromatous histology in pure neuritic leprosy.

Histology was not positive in all patients. False negative results can be attributed to the fact that a) the sural nerve was not affected b) the disease may be in early stages, causing symptoms without showing demonstrable pathological changes, particularly in cutaneous nerves. However, absence of histopathological changes in cases with upper limb involvement alone indicated that biopsy of sural nerve is of doubtful value in that group of PNL patients. In such cases it would be better to take biopsy from other nerves like radial cutaneous nerve. But histological involvement of sural nerve can occur even without clinical involvement as evidenced by obtaining positive nerve biopsy findings in patients who had no clinical involvement of sural nerve.

Relatively few histological studies of skin in pure neuritic leprosy have been published. In this study 40% of patients showed histopathological features suggestive of leprosy. The result was similar to that of a larger study of 196 patients (Suneetha et al 1998). Follow up of patients with PNL shows the development of skin lesions in 29 out of 182 cases as reported by Suneetha et al (2005). Similar observations have also been reported by other investigators (Sharma and Malhotra 2008). This suggests that primary neuritic leprosy may be an early stage of leprosy in a number of cases. This study has also shown that there is a cutaneous component in pure neuritic leprosy and the disease is not totally confined to nerves. Absence of visible skin lesions may be due to the deep location of infiltrate.

PNL presents with features of peripheral neuropathy, however the other causes of peripheral neuropathy need to be excluded like metabolic or nutritional disorders, drug reactions and hereditary diseases. Nerve thickening is also observed in primary amyloidosis of peripheral nerves and certain types of hereditary sensory motor neuropathy (Jopling and McDougall 1995). Investigations such as nerve conduction study may show sensory motor deficits suggestive of leprosy as reported by (Ramadan et al 2001 and combined with other clinical observations can help in clinching the diagnosis of PNL. Other diagnostic methods like fine needle aspiration cytology from affected nerve in expert hands is helpful in diagnosing the disease especially if large nerve trunks are involved (Vijaikumar et al 2001). Recent newer investigations like high resolution ultrasound (Jain et al 2009) is showing promising results in diagnosing leprous neuritis which can also be combined with the skin and nerve biopsies.

In the absence of nerve biopsy, a definite diagnosis of pure neuritic leprosy may not be possible. However thickened peripheral nerves with nerve deficits in patients from endemic areas are diagnosed clinically as pure neuritic leprosy. In our study, none of the patients showed any other pathology which shows the robustness of clinical diagnosis in our settings.

A diagnosis of leprosy implies many associated medical problems, social and psychological trauma to the affected individual. This also necessitates the intake of potentially toxic drugs for long periods. So a diagnosis of leprosy should be made with great accuracy. Hence we strongly recommend the newer investigations and nerve and skin biopsies for the diagnosis of PNL

The main drawback of our study was that the number of patients was small. Biopsy from one of the cutaneous nerve from upper limb could have been a better option in patients having disease limited to upper limb.

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