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Original Article

Pure Neuritic Leprosy in Southern Kerala: Clinico-Epidemiological Characteristics and the Role of Peripheral Nerve Fine Needle Aspiration Cytology as a Diagnostic Aid

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In India, pure neuritic leprosy (PNL) cases constitute a good number of all leprosy cases. There is no single easy method to diagnose PNL. The objectives of this study was to estimate the proportion of PNL, to study the clinico-epidemiological characteristics and peripheral nerve fine needle aspiration cytology (FNAC) findings in PNL. A hospital-based cross-sectional study for a period of 2 years was conducted among leprosy patients. All new clinically diagnosed PNL cases were included. PNL was diagnosed when patients presented with thickened peripheral nerve with sensory loss in the area of its distribution with or without associated motor paralysis, in the absence of any skin lesion and negative skin smears. PNL with single peripheral nerve involvement was defined as paucibacillary (PB) and more than one nerve involvement as multibacillary (MB). Though children <10 years, elderly >80 years and pregnant patients were set as the exclusion criteria, none of the leprosy patients met the exclusion criteria. Relevant socio-demographic and clinical details were noted. Slit-skin smear for acid-fast bacilli, a biopsy from anaesthetic skin, FNAC from the most thickened area of one of the affected peripheral nerves and sural nerve biopsy were done. Findings shows that there were 19 (27.1%) PNL cases among the 70 leprosy patients. The male to female ratio was 5.3:1. The majority (42.2%) belonged to 5th and 6th decades. Sensory loss with motor deficit was the presenting symptom in 52.6%. MB cases constituted 52.6% and PB 47.4%. Ulnar nerve and common peroneal nerves were the most common single nerves affected (21.1% each). Grade 2 disability was seen in 63.2% and foot drop was the most common deformity (31.6%). Multiple deformities were seen in 10.5%. Slit skin smear for AFB was negative in all cases. Findings suggestive of leprosy were observed in 25% of the skin biopsies and in all the eight patients in whom nerve biopsy was performed. Inflammatory infiltrates and/or epithelioid cell granuloma suggestive of leprosy was observed in 57.9% of nerve aspirates. The proportion of PNL and grade 2 disabilities in PNL were high. It is concluded that leprosy workers and medical officers need to be trained regarding the clinical aspects of PNL. FNAC findings suggestive of leprosy were observed in more than 50% of PNL cases. Nerve biopsy needs to be employed only in those with nonspecific findings on nerve FNAC.

Keywords : Neuritic leprosy, Nerve FNAC, Nerve biopsy, Grade 2 disability, AFB.

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Introduction

Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae,* an acid-fast, gram-positive bacillus. It affects the skin and peripheral nerves and is one of the leading causes of preventable deformities. These deformities can lead to stigma and discrimination and are one of the most important barriers in 'accelerating towards a leprosy free world' (WHO 2016). India accounts for about 57.7% of the global leprosy burden (WER 2019). Clinically, leprosy manifests as anaesthetic hypopigmented skin lesions that are easy to diagnose. Pure neuritic (pure neural, primary neural, primary neuritic, polyneuritic) leprosy (PNL) is a type of leprosy that affects only the nerves and manifests as numbness and/or weakness of the muscle supplied by the nerve with absence of skin lesions and negative skin smears (All India Leprosy Workers Conference 1955). Globally, most of the pure neuritic cases have been reported from India (Rao and Suneetha 2016). This type can often remain undetected for many years leading to deformities until acute episodes like neuritis sets in. The cardinal signs of leprosy are – 1) definite loss of sensation in a pale (hypopigmented) or reddish skinpatch 2) thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve and 3) the presence of acid-fast bacilli in a slit skin smear. To diagnose leprosy, at least one of the three cardinal signs should be present (WHO 2006). The diagnosis of PNL, with its absence of skin lesions, is mostly clinical (Dharmendra 1978, IAL 1982, Jardim et al 2003) and one is left with no choice other than applying the second cardinal sign. A grossly thickened nerve is easy to appreciate, but mild to moderate thickening is subject to bias. This can also be confused with other conditions causing mononeuritis / polyneuritis. In such a scenario the definite diagnosis is by nerve biopsy. Many patients may not cooperate for a nerve biopsy and it may not be necessarily free of complications, if from a motor nerve (Jacob and Mathai 1988).

Ours is a tertiary care teaching hospital. Many patients with numbness and/or weakness are referred to us for diagnosis of leprosy. Most of the cases can be diagnosed by applying the second cardinal sign of leprosy, namely, thickened or enlarged peripheral nerve, with loss of sensation and/orweakness of the muscles supplied by that nerve (WHO 2006). Nerve biopsy is indicated in doubtful cases and often patients are apprehensive. A high-resolution ultrasonographic study of the affected nerve is another diagnostic aid, but requires confirmation with a nerve biopsy and is more applicable in impending neuritis (Jain et al 2013). Other investigations like the demonstration of AFB from nerve aspirate by polymerase chain reaction (PCR) (Reja et al 2013) and nerve conduction velocity studies (Ramadan et al 2001) require infrastructure and expertise. Though a multi disciplinary approach would yield the highest level of confirmation in doubtful cases, this may not always be practically feasible.

Fine Needle Aspiration Cytology (FNAC) technique, in general, is a relatively painless, easy and inexpensive procedure compared to tissue biopsy. In our centre, the FNAC report is available within 24 - 48 hours whereas the histopathology report requires a minimum waiting period of three weeks. In the hands of experienced and well-trained practitioners, the accuracy of nerve FNAC in establishing the diagnosis of leprosy equals that of histopathological examinations (Orell et al 1992, Vijayakumar et al 2001). Though nerve FNAC can be performed by the dermatologist as an outpatient procedure, it is not done routinely. With cooperation from the pathology department, where staining procedures are done

on a routine basis, dermatologists can adopt nerve FNAC as an investigation for doubtful leprosy cases in the outpatient clinic.

In this background we decided to conduct a study on PNL patients with the following objectives - 1) to estimate the proportion of PNL among leprosy patients 2) to study the clinico-epidemiological characteristics of PNL 3) to estimate the proportion of grade 2 disability (G2D) among PNL and 4) to determine whether nerve FNAC can be employed for the diagnosis of PNL by comparing with nerve biopsy and skin biopsy from the anaesthetic area.

Materials and Methods

A hospital-based cross-sectional study was conducted for a period of two years at the Department of Dermatology and Venereology, Government Medical College Thiruvananthapuram, Kerala. Institutional ethics committee clearance was obtained. Pure neuritic leprosy was diagnosed, if, while on examination there was a thickened peripheral nerve trunk with sensory loss in the area of its distribution, with or without associated motor paralysis and the absence of any skin lesions regardless of clinical evidence of reactions involving the nerves and negative skin smears (Dharmendra 1978). PNL were categorised into paucibacillary (PB) and multibacillary (MB) based on the number of nerves involved; single peripheral nerve involvement as PB and more than one nerve involvement as MB (NLEP 2013). All new clinically diagnosed PNL cases were included after getting informed written consent. Though non-consenting patients, children < 10 years of age, elderly people > 80 years of age and pregnant patients were the exclusion criteria, none of the PNL patients met these exclusion criteria and thus all PNL patients were included in the study.

The study variables were socio-demographic characteristics like age, gender and occupation and clinical characteristics such as presenting symptoms with duration, previous history of treatment for leprosy, nerve function impairment in the form of sensory loss, number of nerves affected, nerve tenderness, nodularity, thickening, abscess formation, fibrosis, trophic changes and motor deficits. Investigations done were 1) slit skin smear examination from the anaesthetic area, ear lobe and normal skin for demonstration of AFB 2) FNAC from the most thickened part of the affected representative peripheral nerve or any nodular swelling of nerve or from nerve abscess whichever was applicable 3) nerve biopsy from thickened sural nerve or from the sural nerve in that half of the body where nerve thickening was present. The logic for performing nerve biopsy on sural nerve even when it was not thickened was based on the observations (Hui et al 2015 and McDougall et al 1978) that, a biopsy from the sural nerve with its greater number of fascicles resulted in a low false-negative report than nerve biopsy from small sensory cutaneous nerves with their lesser number of fascicles and the report (Shetty et al 2013) that the nerves can be pathologically affected even before appreciable clinical thickening. 4) skin biopsy from the anaesthetic area. FNAC slides, nerve biopsy and skin biopsy specimens were sent to the Department of Pathology for processing and interpretation.

The technique of FNAC: After obtaining consent from the patients, the area of maximum thickness of the nerve was located by palpation. This part was then fixed, the overlying skin cleansed with surgical spirit and a disposable 23 G needle fitted to a 10 cc syringe was inserted into the nerve parallel to the fascicles as to cause minimal damage. The needle when gently moved 2-3

times to and fro over a distance of 2 cm with the plunger of the syringe withdrawn to produce negative pressure, led to aspiration of the inflammatory cells with tissue fluid. After the slow release of negative pressure, the needle with the syringe was withdrawn and the needle dislodged from the syringe. The needle was again remounted to create positive pressure after pulling back the plunger of the syringe, and the aspirated material was pushed on to two clean glass slides and spread with the needle. The smear was fixed with 95% ethyl alcohol for a minimum of 15 minutes for Papanicolaou stain and air-dried for modified Ziehl-Neelsen stain. Papanicolaou stain was used for interpretation of inflammatory cells and Ziel-Neelsen stain for the detecting AFB.

Results

There were 70 leprosy patients and among them, 19 (27.1%) were diagnosed as PNL. None of the PNL patients met the exclusion criteria and hence all PNL patients among the total 70 leprosy patients were included in the study.

There were 16 males and three females with a male to female ratio of 5.3:1. Age ranged from 15 to 64 years. The majority (42.2%) were in the age group of 40-59 years There were three males each in the 2nd, 3rd, 4th, 5th and 6th decade excepting the 7th where there was only one. The three females belonged to 5th, 6th and 7th decade. The age ranged from 15 to 60 years in males and 48 to 64 in females. Manual labourers constituted the majority (6, 31.6%). There were 4 (21.1%) skilled workers and 3 (15.8%) each of students, homemakers and business personnel.

The majority (10, 52.6%) complained of numbness and motor deficit. The other symptoms were numbness (4, 21.1%), numbness with plantar ulcer (2, 10.5%), neuritis (2, 10.5%) and swelling (1, 5.3%). Duration of symptoms ranged from 2 weeks to 10 years (mean 30.3 months). The mean duration of symptoms in those with deformities was 3.2 years and in those without deformities was 11.9 months. Those patients who had presented with deformities initially had numbness for longer duration which they have ignored and consulted health facility only later when the deformities had set in.

There were 2 cases of relapse. As there was no history suggestive of skin lesions of leprosy these patients could have probably been PNL. Both had a history of dapsone monotherapy. One patient presented with plantar ulcer of many years, right foot drop of 4 months and right common peroneal nerve neuritis of 2 weeks duration. The second patient presented with plantar ulcer of 3 months and ulnar clawing of one-month duration. The plantar ulcer may be the sequel of previous disease and ulnar neuritis, the PNL relapse or the patient might have relapsed as PNL MB type with multiple nerve involvement involving upper and lower limbs.

On examination, 10 (52.6%) patients had thickening of multiple nerves and 9 (47.4%) had thickening of a single nerve. Ulnar nerve and common peroneal nerves were the most common single nerves affected (4, 21.1% each). Left-sided nerves were more affected in the upper limbs. The most common affected nerve in the upper limb was left ulnar nerve. In the lower limbs, though equal numbers of nerve were affected on both sides with no side predilection, the most common thickened nerve was the right common peroneal nerve. The patient who presented with swelling had nodular swelling along the course of the great auricular nerve.

Twelve patients (63.2%) had G2D-foot drop in 6(31.6%), claw hand in 4(21.1%) and plantar ulcer in 2 (10.5%). Two out of the six patients with foot drop had plantar ulcer also and that made a

total of 4(21.1%) with plantar ulcer and 2 (10.5%) with multiple deformities. Two patients (10.5%) with plantar ulcer had bilateral distribution.

Investigations:

Slit-skin smears from the ear lobe, anaesthetic skin and normal skin were negative for AFB in all cases.

Nerve FNAC findings are presented in Fig. 1 (a, b, c, d) and summarised in Table 1.

Mononuclear cell infiltrates, either single cell type or in varying combinations were seen in 10 (52.6%) and epithelioid cell collection was seen in one patient (5.3%). One case out of the 10 with mononuclear infiltrates, also yielded AFB. This was a polyneuritic case which yielded scattered lymphocytes and epithelioid cells on nerve FNAC. Eight (42.1%) showed nonspecific findings like neural tissue without any infiltrate, blood and absence of any material.

Nerve biopsy: Histopathology suggestive of leprosy, in the form of either mononuclear cells or epithelioid cells infiltrating the nerve bundles

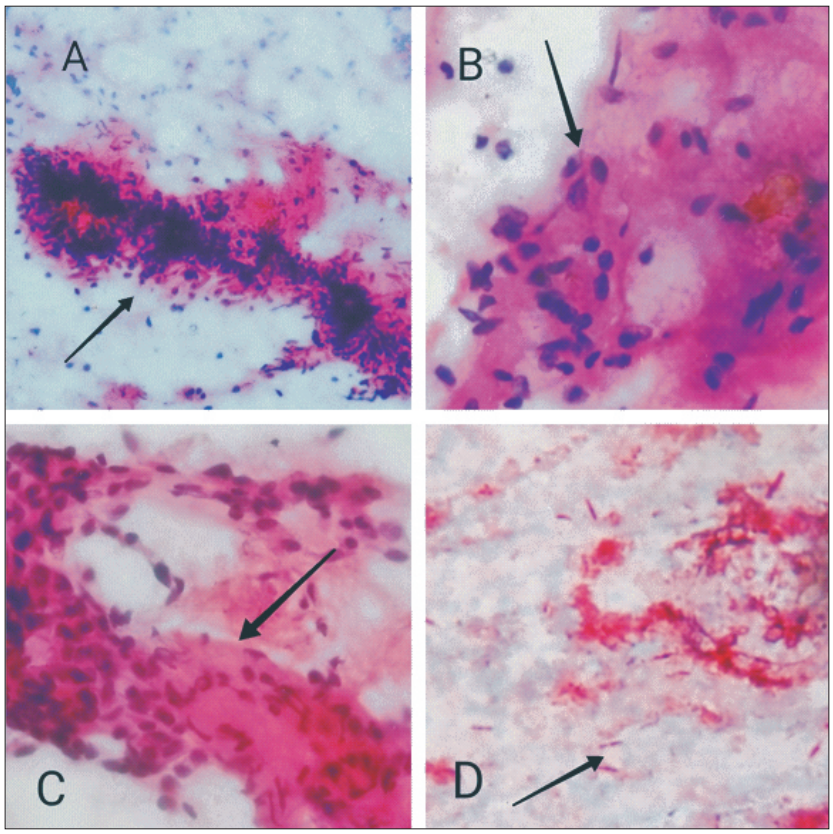

Fig. 1 : Findings from nerve aspirates
A) Epithelioid cell collection and a few lymphocytes (Papanicolaou stain, x 100)
B) Epithelioid cells and occasional lymphocytes (Papanicolaou stain, x 400)
C) Sheets of epithelioid cells and occasional lymphocytes (Papanicolaou stain, x400)
D) Nerve aspirate showing AFB (modified Ziehl-Neelsen stain, x 1000)

Table 1 : Nerve FNAC findings

FNAC findings	Type of PNL		Total (19)
	PB	MB	
Epithelioid cell collection	-	1	1
Scattered lymphocytes	4	2	6
Scattered lymphocytes and epithelioid cells	-	1	1
Scattered lymphocytes and macrophages	-	3	3
Non specific findings (neural tissue without infiltrate, blood, no material)	5	3	8

(Fig. 2), was observed in the nerve biopsy specimens of the eight patients (2 PB and 6 MB) who had consented for nerve biopsy. No AFB was demonstrated on nerve biopsy. Among the 6 MB cases, 5 had sural nerve thickening. The remaining MB case and the 2 PB cases had thickening of the common peroneal nerve.

Skin biopsy: Of the 16 cases who consented for skin biopsy, only 4 (25%) showed perineural mononuclear cell infiltrate suggestive of leprosy (Fig. 3).

FNAC was performed in all the 19 patients, skin biopsy in 16 patients and nerve biopsy in 8 patients. The sensitivity of diagnosis with FNAC alone was 57.9% (11/19), skin biopsy alone was 25% (4/16) and nerve biopsy alone 100% (8/8). As we could not perform nerve biopsy in the remaining 11 patients we cannot confidently comment about our degree of success with nerve biopsy. With either of the two investigations suggestive of leprosy, the sensitivity was 73.6% (14/19) with FNAC and nerve biopsy, 63.2%

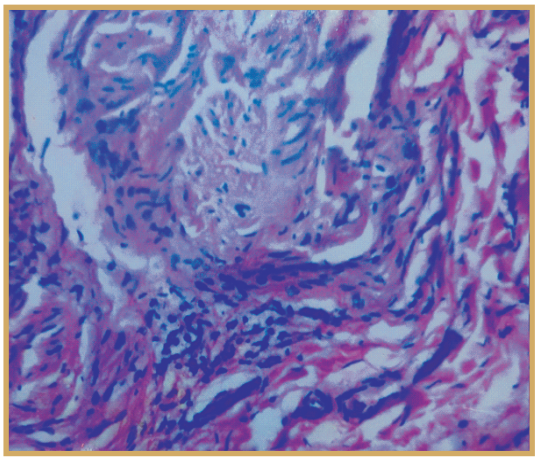

Fig. 2 : Nerve biopsy - Mononuclear cells infiltrating the nerve bundles (H and E, x 400)

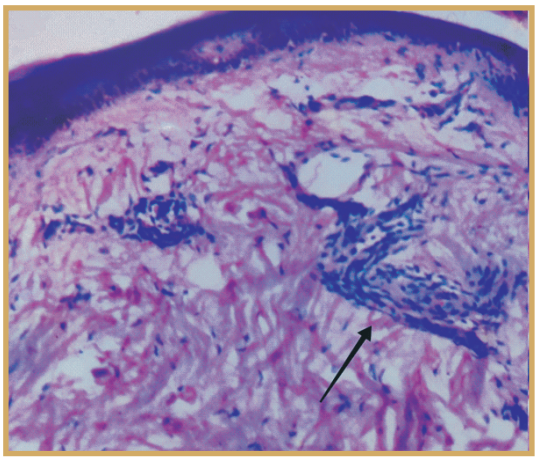

Fig. 3 : Skin biopsy showing perineural mononuclear cell infiltration (H and E, x 100)

(12/19) with FNAC and skin biopsy and (52.9%) 9/17 with a skin biopsy and nerve biopsy. Out of the 19 cases, FNAC suggestive of leprosy was observed in 11 patients and the remaining eight patients with non-specific FNAC findings, skin biopsy was suggestive of leprosy in one and nerve biopsy in three. Thus the sensitivity was 78.9% (15/19) when at least one of the three investigations was suggestive of leprosy.

Discussion

PNL is a well-recognised entity first described from India and has also been reported from other Asian countries, Africa, South America and Europe. PNL can remain undiagnosed leading to deformities and progressive disability.

In the present study, PNL constituted 27.1% of the leprosy cases. Patients are referred to our tertiary care centre from primary and secondary health care setting as well as from other tertiary care centres. The referral nature of the study setting precludes this estimate as a true proportion of PNL compared to estimates from other parts of the country (Dongre et al 1976, Kumar et al 2004, Mahajan et al 1996, Noordeen 1972).

Majority of the patients were male, manual and skilled labourers of the 5^{th} and 6^{th} decade. Literature reports almost similar age (Hui et al 2015, Mahajan et al 1996, Pannikar et al 1983, Kumar et al 2004) and gender distribution (Bryceson and Pfaltzgraff 1990, Hui et al 2015, Kaur et al 1991, Kumar et al 2004, Noordeen 1972, Uplekar and Antia1986).

The presenting symptoms were related to nerve function impairment in 84.2%, manifesting as sensory loss and/ or motor deficit and the consequent trophic changes in the form of plantar ulcer. The mean symptom duration of 30.3 monthsin our patients similar to that reported by George et al (2017) indicates a delay in health care seeking. As people often associate leprosy with hypopigmented anaesthetic skin lesions in PNL, they ignore nerve-related symptoms and present late with deformities (Kumar et al 2004, Williams et al 2019). Frequent case detection campaigns to detect PNL and strategies to increase the community awareness of PNL should be the need of the hour. Despite attending modern medicine and alternative medicine health care facilities, before attending our centre, many remained undiagnosed as leprosy. Periodic training of health workers and medical officers should be conducted to enhance their skills in suspecting, diagnosing and early referral of PNL.

A majority (63.2%) presented late with G2D. The G2D was in the form of a motor deficit in 52.6% and plantar ulcer in 21.1%. Foot drop was the most common motor deficit followed by claw hand. The G2D rate among our patients was higher compared to other studies (Talwar et al 1992, Kaur et al 1991, Kumar et al 2004, Mahajan et al 1996, Mendiratta et al 2006). The referral nature of the study centre well explains the high G2D rate. Literature reports higher deformity rate in PNL compared to other types of leprosy (Kaur et al 1991, Mahajan et al 1996, Talwar et al 1992). The difference in the mean symptom duration of 2.4 years among those with and without deformities in our study highlights the association between longer disease duration and deformities.

Lepra reactions are one of the common presenting symptoms of leprosy. It is a boon in the sense that hitherto unrecognised patients may seek treatment for the first time and is fraught with problems like nerve palsies. Type 1 reaction in PNL may manifest with neuritis, with or without an increase in nerve function impairment, quiet nerve paralysis and nerve abscess (Al-Suwaid et al 1994, Rao and Suneetha 2016). Type 1 lepra reaction in the form of neuritis was the presenting

symptom in 21.1% and half of them had recent onset motor deficit. Type 2 lepra reaction in PNL is rare and may manifest as neuritis and nerve abscess with or without systemic symptoms.

The proportion of our PB and MB cases were approximately equal, 47.4% and 52.6% respectively. However, the majority of PNL cases reported by Kumar et al (2004) and Khadilkar et al (2008) were MB. Though MB type is considered as a risk factor for G2D, in the present study G2D was almost equal among the PB (66.7%) and MB (60%).

Any type of leprosy relapsing as PNL is a vexing problem, as one is quite unsure about the onset of nerve-related symptoms and signs and the initial skin lesions might have already disappeared by the time the patients seeks health care unless there is proper documentation of the original skin and nerve involvement. Pure neuritic leprosy relapsing as PNL has been reported in the literature (Kar and Sharma 2008) and was observed in 10.5% of our PNL cases.

Peripheral nerve FNAC is a simple technique to demonstrate the leprous involvement of the nerve. Nerve aspirate suggestive of leprosy was observed in 57.9%. Scattered lymphocytes (31.6%), scattered lymphocytes and macrophages (15.8%), scattered lymphocytes and epithelioid cells (5.3%) and epithelioid cell collection (5.3%) were the observed findings. One aspirate had AFB along with scattered lymphocytes and macrophages. Translating these observations to Ridley – Jopling classification of nerve aspirate proposed by Vijayakumar et al (2001), our patients with scattered lymphocytes, scattered lymphocytes and epithelioid cells and epithelioid cell collection in FNAC may be considered as towards the tuberculoid spectrum whereas patients with scattered lymphocytes and macrophages and AFB as towards the lepromatous spectrum.

Analysing the correlation between the FNAC findings and clinical classification into PB and MB, PB cases with the yield of scattered lymphocytes in FNAC showed correlation. FNAC of MB cases yielded the findings of both tuberculoid and lepromatous spectrum. This is not surprising as the PB/MB classification is solely for treatment purpose and those who are diagnosed as MB can belong to the tuberculoid spectrum also. Jayaseelan et al (1999) diagnosed PNL in two-thirds of nerve aspirate by the presence of either granulomas or inflammatory cell infiltrate and AFB.

Histopathology findings suggestive of leprosy in the eight patients in whom nerve biopsy was done, stress upon the fact that nerve biopsy is still the gold standard in confirming PNL.

Leprosy is primarily a disease of the nerve and skin involvement occurs later. In the transition phase from nerve to the skin, the anaesthetic skin may show histopathological findings suggestive of leprosy (Suneetha et al 1998, Kumar et al 2004). 25% of the biopsied skin samples had histopathological findings suggestive of leprosy.

FNAC helped us to confirm 57.9% of the clinically diagnosed PNL. Skin biopsy was suggestive of leprosy in 5.2% and nerve biopsy in 15.8% among the remaining patients. A cytological/histopathologic evidence of leprosy was possible in 78.9% of PNL cases when either of the FNAC, skin biopsy and nerve biopsy findings were combined. In doubtful cases of PNL, it is always prudent to go for skin biopsy from the anaesthetic area and a nerve biopsy.

Limitation: The study setting being a tertiary care centre, the findings may not be generalizable to the community. The skin biopsy and nerve biopsy

could not be done in all cases and we had to analyze with the limited numbers.

Conclusion

PNL recognized by the Indian Association of Leprologists (1982) as a subtype of leprosy poses clinical and diagnostic dilemma many a time. Early diagnosis can prevent the development of deformities. The diagnosis is mostly clinical. The confirmatory methods employed in doubtful cases are skin biopsy from the anaesthetic area and nerve biopsy. Though limited, skin biopsy of the anaesthetic area has its own merits. Confirmatory nerve biopsy, being invasive, is not feasible in all cases and not acceptable by many patients. The sophisticated investigations like nerve conduction velocity, high-resolution ultrasonography and nerve aspirate PCR for *M. leprae* may not be feasible in resource-poor settings. Our study has shown that a simple procedure like nerve FNAC can be of help in diagnosing more than 50% of the PNL cases and thus avoid the delay in initiating treatment. The drawbacks of peripheral nerve FNAC such as occasional difficulty in accessing the nerve and scarcity of the aspirate can be overcome with practice. Though there is no single easy method to confirm the clinical diagnosis of PNL, our findings reveal that nerve FNAC can be adopted as the first-line investigation in doubtful PNL cases. Confirmatory nerve biopsy needs to be employed only in those cases where the nerve FNAC findings are not suggestive of leprosy.

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