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Pure Neuritic Leprosy in India: an Appraisal[1]

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ABSTRACT

Background: Pure neuritic leprosy (PNL) constitutes a significant proportion of all cases in India, however, this form of disease has not been fully recognized and investigated and there is little information in the existing literature.

Objective: To study the epidemiological characteristics of PNL in India.

Materials and Methods: A retrospective analysis of leprosy clinic records for the period 1993 to 2003 was undertaken. Detailed demographic profiles and clinical findings were noted from the predesigned clinic proforma. A slit-skin smear for acid-fast baclli (AFB) was done in all cases from the area of sensory loss. A skin biopsy was done from the area of sensory impairment to study histopathological changes. Further investigations such as nerve conduction velocity studies (NCV), fine needle aspiration cytology (FNAC), or nerve biopsy (superficial nerve twigs) were done if indicated in patients whenever there was difficulty in clinical diagnosis.

Results: Of the total 1542 leprosy patients seen over this period, 65 (4.2%) had PNL. Males were more commonly affected than females (2.6:1.). The majority of patients 40/65(61.5%) were aged between 15 and 35 yrs. Predominant presenting symptoms were paresthesia, pain, sensory/motor deficit, and trophic changes. A majority of the patients 39/65 (60.0%) presented with involvement of 2 or more nerves in the same extremity. Mononeuritis was seen in 26 (40%) patients. The nerves most often involved were the right ulnar nerve in the upper extremity, and the right common peroneal nerve in the lower limb. In general, the nerves of the upper extremity were more commonly involved than in the lower limbs (67 vs. 55). Motor deformities such as claw hand and foot drop were present in 13/75 (20%) and 7/65 (10.8%) patients, respectively. Slit-skin smears were negative in all patients, and skin histopathology from the area of sensory loss revealed non-specific inflammation in the dermis in a majority of patients, with perineural inflammation in a few. All patients were treated with multi-drug therapy (MDT); patients with ≥2 peripheral nerve trunk involvements were treated with WHO MDT MB regimen, while others were administered WHO MDT PB regimen. Follow-up for up to 2 yrs was available in only 32/65 (49.2%) patients, none of whom developed any skin lesions during this period.

Conclusion: PNL is a distinct subset of disease frequently seen in India. There is need to pay more attention to this form of leprosy and diagnose and treat patients earlier to prevent deformities and sequelae of nerve damage.

RÉSUMÉ

Background: La lèpre névritique pure (LNP) représente une proportion significative du total des cas observés en Inde. Cependant, cette forme de la maladie n'a pas été complètement caractérisée et reste peu identifiée, avec peu d'information dans la littérature.

Objectif: Etudier les caractéristiques épidémiologiques de la LNP observée en Inde.

Matériel et méthode: Une analyse rétrospective des dossiers cliniques de patients lépreux de l'intervalle 1993–2003 fut entreprise, comportant une extraction détaillée des profils démographiques et des signes cliniques à partir de données présentes dans des fiches cliniques pré-établies standardisées. Un examen bactérioscopique de recherche de bacilles alcoolo-acido-résistants (AAR) fut effectué dans tous les cas, à partir de frottis de suc dermique provenant des aires de perte sensorielle. Une biopsie cutanée fut réalisée à partir des aires de perte sensorielle afin d'étudier les changements histopathologiques. Des investigations complémentaires, telles que des études de vélocité de conduction nerveuse (VCN), des aspirations à l'aiguille fine (AAF) en vue d'examens cytologiques, ou des biopsies

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nerveuses (rameaux nerveux superficiels), furent mises en œuvre dès que des difficultés de diagnostic clinique le justifiaient chez certains patients.

Résultats: Soixante cinq parmi 1542 patients lépreux (4,2%) présentaient une LNP. Les hommes étaient plus communément affectés que les femmes (2,6:1). La majorité (40/65 ou 61,5%) était âgée de 15 à 35 ans. Les symptômes prédominants à l'examen initial étaient des paresthésies, des douleurs, des déficits moteurs et/ou sensoriels et des altérations trophiques. La majorité des patients (39/65 soit 60,0%) présentaient une atteinte de 2 nerfs ou plus innervant le même membre. Les mono-névrites ne furent observées que chez 26 (40,0%) des patients. Les nerfs les plus communément atteints étaient le nerf ulnaire droit pour les membres antérieurs et le nerf péroné commun pour les membres intérieurs. En général, les nerfs des membres antérieurs étaient plus communément atteints que ceux des membres postérieurs (67 versus 55). Les difformités d'origine motrices, telles que les mains en crochet et les pieds tombants, ont été observées chez 13/65 (20%) et 7/65 (10,8%) des patients, respectivement. L'examen bactérioscopique à partir de suc dermique fut négatif chez tous les patients atteints de LNP, et l'examen histologique de la peau provenant de zones avec perte sensorielle n'a révélé qu'une inflammation non spécifique du derme chez la majorité des patients, avec une inflammation péri-nerveuse dans quelques cas. Tous ces patients furent traités par une poly-chimiothérapie (PCT) ; les patients présentant une atteinte de 2 nerfs ou plus furent soignés par le traitement recommandé par l'OMS concernant les patients multibacillaires, tandis que les autres reçurent le traitement des patients paucibacillaires. Un suivi ne dépassant pas 2 années n'était présent que chez seulement 49/65 (49,2%) des patients. Ces derniers n'ont pas développé de lésions cutanées durant cette période.

Conclusion: La LNP est une catégorie distincte de la lèpre qui est assez fréquemment observée en Inde. Il va être nécessaire de prêter une plus grande attention à cette forme de la maladie afin de diagnostiquer et traiter les patients plus précocement, ce qui devrait permettre de prévenir les difformités et séquelles secondaires aux lésions nerveuses.

RESUMEN

Panorama: La lepra neurítica pura (LNP) constituye una significante proporción de todos los casos de lepra en la India, sin embargo esta forma de la enfermedad no se ha estudiado con el detalle requerido y por esto casi no hay información al respecto en la literatura.

Objetivo: Estudiar las características epidemiológicas de la LNP en la India.

Materiales y Métodos: Se realizó un análisis retrospectivo de la lepra en los archivos clínicos correspondientes al periodo de 1993 a 2003. Los perfiles demográficos detallados y los hallazgos clínicos fueron concentrados en un formato prediseñado. En todos los casos se buscaron bacilos ácido resistentes en la linfa cutánea de las regiones con pérdida sensorial y también de estas regiones se tomaron biopsias para su estudio histopatológico. En los pacientes con diagnóstico clínico impreciso se hicieron además otros estudios tales como medición de la velocidad de conducción nerviosa (VCN), citología por aspiración con aguja fina (CAAF), o biopsia de los nervios superficiales.

Resultados: Del total de 1542 pacientes con lepra vistos en este periodo, 65 (4.2%) tuvieron PNL. Los hombres fueron más afectados que las mujeres (2.6:1). La mayoría de los pacientes 40/65 (61.5%) tuvieron entre 15 y 35 años. Los síntomas más aparentes fueron parestesia, dolor, déficit sensorial/motor, y cambios tróficos. La mayoría de los pacientes 39/65 (60%) presentaron involución de 2 ó más nervios en la misma extremidad. Veintiséis pacientes (40%) tuvieron mononeuritis. Los nervios más frecuentemente afectados fueron el ulnar derecho en la extremidad superior y el peroneal común derecho en la extremidad inferior. En general, los nervios de la extremidad superior fueron más frecuentemente afectados que los nervios de la extremidad inferior (67 *vs* 55). Las deformidades motoras tales como mano en garra y pie caído estuvieron presentes en 13/75 (20%) y 7/65 (10.8%) pacientes, respectivamente. Los extendidos de linfa cutánea fueron negativos en todos los pacientes y la histopatología del área anestésica no reveló inflamación inespecífica en la dermis en la mayoría de los pacientes, aunque algunos presentaron inflamación perineural moderada. Todos los pacientes fueron tratados con poliquimioterapia (PQT); los pacientes con afección de dos o más troncos nerviosos periféricos fueron tratados con el régimen de PQT de la OMS para la lepra multibacilar. El seguimiento por 2 años sólo se pudo hacer en 32/65 (49.2%) pacientes, ninguno de los cuales desarrolló ninguna lesión en la piel durante este periodo.

Conclusión: La LNP es un tipo particular de la enfermedad frecuentemente observado en la India. Es necesario poner más atención a esta forma de la lepra con objeto de diagnosticar y tratar a los pacientes de manera temprana para prevenir las deformaciones y secuelas del daño a nervios.

Nerve damage and the consequences of nerve damage set leprosy apart from other diseases. Leprosy would be a rather innocent skin disease were it not for the nerve damage and subsequent deformities, which make the leprosy patient an outcast from society. Considering the central place that nerve damage occupies in leprosy and in the personal and social consequences of the disease, it is perhaps surprising how little importance its recognition and treatment is given in most elimination campaigns, where the emphasis is very much on MDT only ([11]). Nerve involvement, whether clinical or microscopic, is fundamental to the pathogenesis of leprosy, and it should receive more attention in the elimination program to reduce the burden of deformities in the community. Although both skin and nerve involvement usually occur together in leprosy, there can also be nerve involvement without any primary skin lesion. This form of disease has been called neuritic leprosy (pure neural, primary neural, pure neuritic, primary neuritic, polyneuritic) ([2]). Although such patients constitute a significant proportion of all cases, especially in India, this category of patients has not been fully recognized or thoroughly investigated, with scarce published information in the literature ([3, 10, 12, 15, 16, 20, 26, 27]).

The Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, is a tertiary care center in Northern India, which is a low endemic area for leprosy. In addition to the population of this region, the Institute also caters to a large migrant population from various states of the country where leprosy is endemic. Systematic analysis of the leprosy clinic records at our center was carried out to study various epidemiological characteristics of patients with pure neuritic leprosy (PNL) over a period of last 10 yrs.

MATERIALS AND METHODS

Clinic records of patients diagnosed as PNL enrolled at our center from 1993 to 2003 were analyzed. PNL was defined as thickened peripheral nerve trunk with sensory loss in the area of its distribution, with or without associated motor paralysis in the absence of any skin patch regardless of clinical evidence of reaction involving nerve(s) ([2]). Detailed demographic profile and clinical findings were recorded in the predesigned clinic proforma. Slit-skin smear for acid-fast baclli (AFB) was done in all cases from the area of sensory loss. It was ensured by at least two observers that we were not missing any skin lesions. A skin biopsy was done from the area of sensory impairment to study histopathological changes. Further investigations like nerve conduction velocity studies (NCV), fine needle aspiration cytology (FNAC), or nerve biopsy (superficial nerve twigs) were done if indicated in patients whenever there was difficulty in clinical diagnosis. All patients were treated with multi-drug therapy (MDT). Patients with ≥2 peripheral nerve trunk involvements were treated with WHO MDT MB regimen while others were administered WHO MDT PB regimen. All patients with recent onset of motor deficit within the preceding year were treated with a 6 month course of oral prednisolone in tapering doses. All reaction episodes were managed with oral corticosteroids given over 12 to 16 week period. Patients were instructed to report for follow-up twice a year for at least two years after completing therapy or immediately in case of any symptom suggestive of acute neurological deficit. The objective of the present study was to analyze epidemiological features of PNL such as their frequency, age and sex distribution, presenting symptoms, number of nerves involved, common sites of nerve involvement, deformities, and evidence of reactions etc.

RESULT

Of the total 1542 leprosy patients seen over this period, 65 (4.2%) had PNL. In 9 patients with nerve thickening but equivocal neurological deficit, the diagnosis was confirmed by NCV studies. In addition, in 2 patients it was supported by FNAC and nerve biopsies. The age and sex distribution of patients with PNL is given in Table 1. Males were more commonly affected than females (2.6:1.). The majority of the patients 40/65(61.5%) were aged between 15 and 35 yrs. Most of the patients with PNL presented to us with more than one symptom. Predominant presenting symptoms were paresthesia, pain, sensory/motor deficit, and trophic changes (Table 2). A majority of the patients 39/65 (60.0%) pre-

TABLE 1. *Demographic parameters of patients.*

Age	Sex M/F	Total
≤14	4/0	4
15–25	15/6	21
26–35	12/7	19
36–45	7/2	9
46–55	5/3	8
≥56	4/0	4
Total	47/18	65

sented with involvement of 2 or more nerves in the same extremity. Mononeuritis was seen in 26 (40%) patients. Involvement of more than one limb was not uncommon, and up to 7 nerves were involved in 6 (9.2%) of the 65 patients. The nerves most often involved were right ulnar nerve in the upper extremity, and the right common peroneal (lateral popliteal) nerve in the lower limb. In general, the nerves of the upper extremity were more commonly involved than those in the lower limbs (67 vs. 55) (Table 3). Slit-skin smears from all sites including the area of anesthesia were negative for AFB in all the patients. Skin histopathology revealed non-specific inflammation in the dermis in a majority of patients with perineural inflammation in a few. However, no well-formed granuloma or AFB were discernable in any skin biopsy specimen.

Twenty patients had symptoms suggestive of neuritis in the form of pain and paresthesia along the distribution of affected nerve trunk. Motor deformities such as claw hand and foot drop were present in 13/75 (20%) and 7/65 (10.8%) patients, respectively. Of these 13 patients, 11 had partial (ulnar) and 2 had complete (ulnar + median) claw hand. Various trophic changes in

TABLE 2. *Presenting symptoms. (Many patients presented with more than one symptom.)*

Symptoms	No. of Patients
Paresthesia	10
Pain in the area supplied by the nerve	20
Sensory deficit	43
Motor deficit	20
Trophic changes	10

TABLE 3. *Sites of nerve involvement.*

Nerves involved	Number and location of nerves involved	
	Right	Left
Ulnar	30	14
Median	2	4
Radial	0	1
Radial cutaneous	8	8
Common peroneal	16	12
Posterior tibial	12	9
Sural	4	2
Greater auricular	3	3

the form of trophic ulcers, xerosis, fissured hands and soles were seen in 10 (15.4%) patients. More patients had plantar ulcers, 8/10 (80%), than those over hands, 2/10 (20%); 5 of them had more than one trophic ulcer.

Sixteen (24.6%) patients had motor deficit of recent onset, and treatment with oral prednisolone resulted in significant improvement in 6 months. All patients 20/65 (30.8%), who had neuritis [painful tender nerve(s) with paresthesia or sudden increase in anesthesia] at the time of presentation, and 4/65 (21.5%) patients who developed it during treatment with MDT responded well to a course of systemic steroids. Two patients (3%) had an abscess in the ulnar nerve, which was managed by surgical drainage along with MDT and prednisolone.

Only one of our patients (on MDT PBR) developed multiple skin lesions during the treatment, and responded well to MDT MBR. Follow-up of up to 2 yrs was available in only 32/65 (49.2%) patients, none of whom developed any skin lesions during this period.

DISCUSSION

Although its overall prevalence is decreasing, leprosy continues to be a major cause of neuropathy and a significant cause of disability worldwide ([14]). PNL is a well-recognized clinical entity in India ([2, 15]). It is characterized by neural signs manifested by an area of sensory loss along the distribution of a thickened nerve trunk with or without motor deficit and absence of any skin patch ([15]). Experimental evidence has suggested that *Mycobacterium leprae* can

gain entry through skin ([9]) as well as through upper respiratory tract ([1]). Talwar, *et al*. ([26]) proposed that entry through the skin produces mononeuritic type of disease, while the respiratory route may be responsible for the polyneuritic type of disease. It is postulated that after entering through the skin, *M. leprae* invades axoplasmic filaments and only after rupturing Schwann sheath the organism can burst into the corium of the skin ([2]). PNL may be an early stage in the pathogenesis of the disease before the appearance of skin lesions. Roche, *et al*. ([19]) investigated the serological response to two *M. leprae* specific epitopes (PGL-1 and 35K Da protein) in 46 untreated patients with PNL. They reported a significant increase in the level of antibody response (IgM) when more nerve trunks were involved. Changes in antibody levels in seropositive PNL patients may prove useful in monitoring the response to chemotherapy.

The occurrence of PNL shows marked regional variations. PNL is frequently seen in India, while it is much less common in some other countries. According to Noordeen ([15]), PNL contributes up to one-sixth of all leprosy cases in India. Frequency of its occurrence varied from 4.6% ([12]) to 5.5% ([3]) in western India to 17.7% in South India ([15]). Some cases may be misdiagnosed, so available figures may be lower than the actual proportion of cases in the community. In our study (North India), PNL accounted for 4.2% patients. In most of the earlier studies ([12, 15, 16]), the majority of cases were aged above 40 yrs. Noordeen ([15]) observed steadily rising incidence with increasing age. In contrast to previous reports, a majority of patients in our study were between 15 and 35 yrs of age. This could be attributed to an increased level of awareness about the disease in the general population and relatively early detection of cases because of elimination campaigns in the last decade, or to regional variation in the epidemiology of disease. As observed earlier ([12, 15, 16]), this form of leprosy is relatively uncommon in children, in our study children constituted only 6.1% of the total patients. Like us, some previous workers ([10, 15, 27]) also observed male preponderance in PNL as is present even in other types of leprosy.

Mononeuritis has been the most common presentation in some of the previous studies ([12, 15, 27]), where as in our study, involvement of two nerves of the same extremity was the most frequent finding (60%) and mononeuritis was seen in 40% of our patients. Involvement of multiple nerves at the time of presentation has also been highlighted by some other workers ([12, 16]). As observed by us, a majority of the previous reports ([12, 16, 26, 27]) have also noted ulnar nerve to be the commonest affected nerve in PNL. However, Noordeen ([15]) reported the lateral popliteal nerve to be most commonly affected in PNL.

Pure neuritic cases are probably more vulnerable to nerve damage as supported by a high frequency of deformities reported by various workers ([10, 12, 26]). This could be because of more delay in diagnosis of PNL patients than those with skin lesions. So it is important to recognize the symptoms early. Unfortunately patients usually ignore or misinterpret the symptoms and present rather late, after significant nerve damage has already occurred; 20 (30.7%) of our patients presented with a predominant motor deficit, which is a rather late occurrence. Deformities in leprosy could be secondary to nerve involvement in untreated disease or because of reactions. Though grading of deformities may vary at different centers, a high deformity rate in PNL has been reported in many studies [Talwar, *et al*. 16.1% ([26]), Kaur, *et al.* 31.5% ([10]), Mahajan, *et al*. 48.6% ([12])]. Reactions in the form of neuritis at the time of presentation or during the treatment were seen in 34/65 (52.3%) of our patients. No definite figures on reactions are available in other series on PNL. Nerve abscess, when present, makes clinical diagnosis of PNL easy. Though there are isolated case reports ([21]), the frequency of its occurrence in other large series on PNL has not been reported.

Diagnosis of PNL can be mostly made on clinical examination in a majority of the cases, especially in endemic areas ([2, 8, 23]). Although nerve biopsy is ideal for diagnosis, it is often not practicable and has its own limitations ([7, 13]). Recently polymerase chain reaction (PCR), FNAC and various electrophysiologic studies have been reported to be useful laboratory adjunct in confirming diagnosis of doubtful cases ([8, 18, 28]). However,

the expertise for the technique and sensitivity of this test are the limitations. The importance of a biopsy from normal looking anaesthetic skin is to exclude the possibility a cutaneous leprosy lesion which may not be clinically apparent, although histopathologically the evidence can be convincing ([5]). Findings in the apparently normal skin and nasal mucosa in patients with the diagnosis of PNL indicate that there are widespread changes due to leprosy even when the disease appears clinically confined only to a few nerves ([24, 25]). Suneetha, *et al*. ([24]) reported histological changes of leprosy in the apparently normal looking skin of 32.1% patients of PNL, with 12.7% of them having either epithelioid or macrophage granulomas. They proposed that absence of visible hypopigmented skin lesions in these patients is probably related to the deep location of the granuloma in the dermis, beyond the scope of exercising any direct influence on the melanocytes in the epidermis. However, similar to our observations, Kaur, *et al*. ([10]) did not find any significant pathology in the anesthetic skin of patients with PNL.

There are no defined WHO guidelines about the classification of these cases and therefore, about treatment ([6]). Many of these cases are simply considered to belong to the PB group since all of them are SSS negative and are mostly lepromin positive ([2]). However, nerve biopsy in several cases has revealed features of borderline or even lepromatous spectrum with large number of bacilli ([10,16]). Unlike skin lesions, it is not possible to routinely carry out invasive investigations (biopsy, smear, etc.) in patients with PNL to classify the disease for treatment purposes. The number of nerve trunks involvemed can be taken as a reliable clinical criterion for determining the MDT regimen (PB/MB).

The long-term course of PNL is not fully clear. Noordeen, in his field observations from South India, reported that there is a tendency for spontaneous resolution of some cases of PNL ([15]). However, this observation has not been made by others. Subsequent development of skin lesions (most commonly, borderline tuberculoid) is well known, with many case reports in the published literature ([15, 16, 17, 22, 24, 27]). In a study by Talwar, *et al*. ([26]), 25% and 7% of their PNL patients treated with dapsone monotherapy and MDT PBR developed skin lesions at an average period of 3 and 2.6 months, respectively. In a study from South India ([24]), 15.9% patients with PNL developed skin lesions during follow up period varying from 6 months to 12 yrs. However, Mahajan, *et al*. ([12]) did not report skin lesions in any of their patients followed up to 18 months after stopping MDT. It has been suggested that this phenomenon is more likely in those patients of PNL, who are not treated adequately or when treatment is irregular, whereas, prompt and better killing of the organisms by adequate MDT arrests the spread of disease from the nerves to skin preventing development of skin lesions ([26]). Only one of our patients (on MDT PBR) developed skin lesions during the course of anti-leprosy treatment, and was later treated with MDT MBR. In addition, the possibility of developing new skin lesions during treatment as part of a reversal reaction should be kept in mind ([4]).

Although a lot has been achieved towards eliminating leprosy, there is yet a long way to go. We should ensure that during this transition from dedicated leprosy programs to their amalgamation with general health services, adequate awareness and expertise about the timely diagnosis and treatment of this neural phenomenon is maintained, as such cases will probably continue to occur sporadically in the "post-elimination era."

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