EDITORIAL

Pure or Primary neuritic Leprosy (PNL)

BHUSHAN KUMAR*
*H No. 81, Sector 16-A, Chandigarh 160 015, India

Accepted for publication 17 November 2016

Introduction

Leprosy is primarily a disease of the nerves. Mycobacterium leprae infects the Schwann cells (SC) that surround the nerve fibres and axons. Leprosy is a complex disease known for having great variability in its clinical presentation, sometimes with more nerve involvement and related anesthesia and deformities and sometimes with skin lesions primarily. In about 4–8% of the cases the clinical presentation is exclusively with nerve involvement in the form of nerve deficit or nerve thickening, without any cutaneous lesions, with a negative skin smear and no other identifiable pathology. This is commonly known as pure neuritic leprosy (PNL) and is more common in the Indian subcontinent. In India the incidence varies from 5·5 to 17·7% of all leprosy cases.1,2

The most common presentation of PNL is a mononeuritis (single nerve involvement) which occurs in about 60% of the cases.3 When more than one nerve is involved in an asymmetrical distribution it is known as mononeuritis multiplex, while symmetric involvement is called polyneuropathy or symmetrical polyneuritis. Nerves in the upper limbs (ulnar, radial cutaneous) are involved more often, and temperature and pain sensation are the first to be affected, but the patient may complain of sensory and/or motor impairment, numbness, parasthesiae and neural pain.4–6

Prevalence

Wade7 in an Editorial in 1952 mentioned the recognition of polyneuritic leprosy by the International Symposium on Leprosy. The assessment of 20,000 patients from six continents during a 28 year period showed that neurological manifestations as mononeuritis or mononeuritis multiplex are common and may precede cutaneous lesions by several months.8 In an epidemiologic study on 8,000 patients with leprosy, 106 (8·2%) patients were diagnosed with PNL.9 Dongre et al.10 studied 11,581 patients and 5·5% were found to have PNL. In a Brazilian study PNL was diagnosed in 34 of the 162 nerve biopsies studied.11
Jardin assessed 49 patients with PNL and observed mononeuritis multiplex in 61%, mononeuropathy in 33% and only 6% had polyneuropathy. In another assessment on 19 and 21 patients, sensory and motor losses, neural thickening and neural pain were the predominant presentation. Sixty-seven patients with PNL underwent biopsy of dorsal cutaneous branch of the ulnar, sural and superficial fibular nerves. Acid fast bacilli (AFBs) were seen in 16% of them, with a PCR test for *M. leprae* being positive in 47%.12 Thirty three patients suspected of PNL were followed from 1994–2004. Nerve biopsy confirmed leprosy in 11 (33.3%) of them.5

**Diagnosis**

Most of these patients present with nerve function impairment (NFI) (sensory or motor or both) and usually present to the internists or neurologists, as there are no skin lesions. A high degree of clinical suspicion is required for making the diagnosis of PNL. A wide range of differentials has to be considered as there are no absolutely diagnostic clinical features of leprous neuropathy. Although nerve thickening is a soft pointer, there are other rare conditions in which a patient presents with NFI and thickened nerves. Other causes of neuropathy that should be excluded are metabolic (diabetes mellitus, amyloidosis, toxic, nutritional); infectious (syphilis, HIV associated, poliomyelitis, Lyme disease); inflammatory (sarcoidosis); congenital or hereditary (Charcot Marie Tooth disease, syringomyelia, congenital insensitivity to pain, hereditary neuropathy), traumatic or postural (acute and chronic compression) and tumoral (neural sheath tumour).

A complete skin examination and slit skin smear (SSS) should be done in all the cases. Some patients with symmetrical neuritis present with ‘glove and stocking’ hypoesthesia or anaesthesia and skin changes suggestive of autonomic neuropathy which is difficult to differentiate from early lepromatous leprosy. Hence a SSS is essential before the complete sensory and motor evaluation. Then a battery of tests including blood glucose, ANA, ANCA, HIV, HBsAG and Anti HCV, are done to exclude other causes of peripheral neuropathy.

Even after complete neurological examination and biochemistry the diagnosis of PNL can only be established by demonstration of AFB in the nerve. Nerve biopsy is the gold standard for diagnosis of PNL. However nerve biopsy is fraught with the risk of nerve damage, poor sampling (not hitting the involved area) and low sensitivity.13 Preferably a purely sensory nerve supplying the area of involvement should be biopsied, AFB however, are not found in all cases. In the absence of molecular diagnostic facilities other features that help in the diagnosis of PNL are the presence of epithelioid cell granuloma, perineural expansion, endoneural infiltrate, endoneural and perineural fibrosis and a reduction in the number of myelinated nerve fibres. Immunochemistry can be added to the routine histopathology and immunolabeling of lipoarabinomannan (LAM) or phenolic glycolipid 1 (PGL-1) can be studied in the biopsy specimens. Fine needle aspiration cytology (FNAC) of the nerves is a relatively simple and minimally traumatic procedure which is a preferred modality before performing a nerve biopsy as the results are comparable with nerve biopsies.14 Polymerase chain reaction (PCR) on tissues from nerves can help in the diagnosis in AFB negative material.

The positivity of Mitsuda skin test in patients with PNL ranges from 57.1 to 100%.5,15 Though of poor diagnostic value, the Mitsuda test together with clinical, serological, morphological and histopathological data helps in the operational classification of patients with PNL.
Serology can be of help especially in the multibacillary part of the spectrum and a rapid diagnostic test (ML Flow) detects antibodies against PGL-1. This test can also be used to assess the response to treatment as the antibody titre should fall after successful treatment. Though it can be a good tool to monitor therapy, it is not specific to neuritic leprosy.

Electrophysiological studies can be used both for diagnostic and monitoring purposes. Nerve conduction studies (NCS) detected changes in 40% of the patients who had silent neuropathy. Common findings were dampening of sensory nerve action potentials (SNAP) and compound motor action potential (CAMP) which indicate axonal damage and decreased sensory conduction velocity as reported in the INFIR study. Additionally increased latency and temporal dispersion indicate demyelination. These alterations precede nerve function impairment and are more sensitive than monofilament test and voluntary muscle testing. Quantitative sensory testing enables thermal testing of unmyelinated C fibres and myelinated Aβ fibres mediating cold sensation. Vibrometry can assess large myelinated Aβ fibres.

Annex

Clinical signs and symptoms suggestive of neuropathy

In a high endemic zone, always consider Pure Neuritic Leprosy as a differential

Consider differentials

Metabolic (diabetes, amyloidosis)
Infectious (HIV, syphilis, HBV, HCV)
Inflammation
Congenital (Charcot Marie Tooth, Syringomyelia)
Traumatic
Tumoral (Nerve sheath tumor)

Clinical Examination

1. Palpate for enlarged nerves
2. Examine the whole body for skin lesions
3. Performs sensory test for thermal sensation, pain and touch
4. Test sensation on distribution of the nerve with Semmes Weinstein monofilament
5. Voluntary Muscle Testing

Slit Skin Smear to look for AFB

Electromyography
Changes can be demyelinating type, axonal type or mixed

High Resolution Sonogram and Colour Doppler
Nerve enlargement is picked up with higher sensitivity
Increase flow in colour Doppler indicates extensive inflammation and nerve damages
Currently high resolution ultrasonography (HRUS) and color Doppler (CD) are being evaluated to assess the thickness and vascularity of the nerves. Thickness assessed by HRUS has higher sensitivity than clinical examination and can help in identifying the nerve to be biopsied.\textsuperscript{20,21} CD shows increased vascularity of nerves that are extensively damaged or are in reaction. Both HRUS and CD are useful tools in the diagnosis of PNL.

Considering the difficulty in making a definite diagnosis especially in non-specialist settings, an algorithm has been suggested which may be applied depending upon the availability of investigative facilities and will help to decide between the diagnosis of ‘definite pure neuritic leprosy’ or of ‘probable pure neuritic leprosy’. (Annex)

**Evolution and Natural History**

Studies on leprosy neuropathy have shown that even in the presence of skin lesions, there may be a mismatch in the severity/classification of disease in the nerves vis-à-vis skin. Thus the disease may be paucibacillary in the skin, but multibacillary in the nerves.\textsuperscript{22} PNL precedes the development of cutaneous lesions in 15–35% of the cases\textsuperscript{16,22,23} so close follow-up is essential because reactions may develop in many of them which will help in revising the diagnosis and treatment. Talwar et al. followed 62 patients with PNL and eight of them (13%) developed cutaneous lesions within 6 months of starting therapy.\textsuperscript{24} In a follow up of 182 patients with PNL 29 patients (15.9%) developed cutaneous lesions within 6 months of starting therapy.\textsuperscript{23} It was found that a large proportion of patients (51.8%) developed lesions while on MDT and 13.7% developed cutaneous lesions during RFT. Some authors did not find histopathological alterations in the anesthetic areas while others found skin biopsy to be abnormal in approximately 30% of the cases.\textsuperscript{25–27} Cutaneous lesions covered almost the whole spectrum of leprosy (indeterminate BT and BL). The absence of cutaneous alterations on histology does not exclude the diagnosis of PNL, but as it is less invasive than the nerve biopsy, skin biopsy should be the first option.

**Treatment**

PNL needs to be classified as either paucibacillary (PB) or multibacillary (MB) for treatment purposes. The disease is classified as PB when only one nerve is involved and MB when two or more nerves are involved, although histopathological changes representing the entire spectrum of classification (Ridley-Jopling Classification) of PNL have been described.\textsuperscript{1,14} Nerve damage in leprosy can lead to lasting consequences of disability. MDT does not halt the progression of nerve damage and often patients end up with more disability after MDT. We have to consider the nerve damage the patient has at the time of diagnosis and also the nerve damage which can result from reactions which have to be managed rather aggressively. Prescription of steroids for reactions or in cases of recent onset of NFI (< 6 months) is well recognised, but prophylactic use of steroids in all patients is debatable. In a study on PNL patients, significant improvements in sensory-motor clinical parameters and electrophysiological studies were observed over a period of 1 year in those given adequate doses of oral steroids for 6 months.\textsuperscript{28}

There are no well established data regarding the proportion of patients of PNL who may go into reaction, so all patients with PNL should be monitored closely for a minimum period
of 2 years and longer if possible. Extension of the area of anesthesia would mean either the worsening of the disease or development of a reaction.

Relapse will be defined by the presence of new signs and symptoms or new finding of AFBs in skin or nerve biopsy. Relapse rates after MDT are typically low (<1%), but may be higher, depending on the treatment regimen, duration of follow up and if it was determined by physical examination, skin smear or biopsy.29

Another aspect of management of PNL is neuropathic pain, which can be disabling and requires anti-epileptics such as pregabalin or gabapentin, or tricyclic antidepressants such as amitriptyline or nortriptyline. Despite all this a subset of patients continues to suffer from this pain and some researchers are of the opinion that microneurolysis may benefit these patients.

Conclusion

In summary, PNL is a definite clinical entity with subtle findings, which is diagnosed by clinical, histopathological, bacteriological, electrophysiological and ultrasound criteria. Early diagnosis and prompt institution of treatment is required for better functional recovery and prevention of disabilities. The MB regimen may be a better option because even in a patient with clinically-apparent involvement of only one nerve, other nerve(s) may also be involved subclinically. Electrophysiological tests are sensitive modalities for picking up this subclinical neuropathy and should ideally be done in all cases. Skin biopsy and nasal mucosal biopsies yielding positive results in 32.1% and 51% respectively27,30,31 would suggest that PNL is the earliest presentation which may not show any changes in the overlying skin or AFB positivity on SSS, but it is ultimately likely to evolve into a more widespread disease – which may further justify the institution of MB therapy.

Development of cutaneous lesions in pure neuritic cases positively indicates the natural history of the disease, conforming to the hypothesis that leprosy is basically neural in inception and that all other forms emerge from it.

Acknowledgements

Special thanks to Dr. Shraddha Uprety, Lecturer, CMCTH, Chitwan, Nepal in helping me with the collection of material and style of presentation.

References

9 Noordeen SK. Epidemiology of (poly) neuritic type of leprosy. Lepr India, 1972; 48: 132–137.