# Primary Neural Leprosy

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## 16.1 Introduction

Leprosy is a multisystem disease that mainly affects tissues originating from the embryonic ectoderm: skin and peripheral nerves. It is clinically diagnosed by three cardinal signs: loss of sensation in skin lesion, enlarged nerves, and positive skin smear [1]. Two out of these three signs are needed to make a definite diagnosis. However, leprosy without skin lesions and with a negative skin smear, showing nerve lesions only, does exist, being known as primary neural leprosy or pure neural leprosy. Primary neural leprosy (PNL) is well known from the Indian subcontinent, where it constitutes 2–10% of newly diagnosed patients, depending on the area, the quality of the leprosy program, and the interests of leprologists [2–5]. During the past decades, it has been diagnosed outside India as well, partly due to increased awareness, in 1–4% in Brazil [6–8], 1–2% in Senegal, and 1–2% in the Netherlands.

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**Table 16.1** Signs and symptoms of primary neural leprosy in the region of nerve distribution

| |
|---|
| • Loss of sensation |
| • Loss of muscle strength |
| • Loss of sweating |
| • Neuropathic pain: paraesthesia, paroxysmal pain |
| • Dysesthesia and allodynia |
| • Painful nerves |
| • Enlarged nerves |
| • Visible nerves |

**Table 16.2** Differential diagnoses of enlarged nerves

| **Acquired neuropathies** |
|---|
| • Leprosy |
| • Acquired amyloidosis |
| • Chronic inflammatory demyelinating neuropathy and its variants |
| • Multifocal motor neuropathy |
| • Acromegaly |
| • Nerve tumours |
| **Inherited neuropathies** |
| • Hereditary motor and sensory neuropathies (Charcot–Marie–Tooth (CMT)1A, CMT1B, CMT1E neuropathy, Dejerine–Sottas neuropathy, hereditary neuropathy with liability to pressure palsy (HNPP)) |
| • Refsum disease |
| • Inherited amyloidosis (TTR, PRPN) |
| • Neurofibromatosis |

## 16.2 Diagnosis

The diagnosis is not easy and is often missed when not suspected [7–9]. PNL should always be considered in differential diagnosis when there are signs of neuropathy in patients who have lived in or come from endemic countries. The manifestations of pure neural leprosy are those found in most neuropathies, including loss of sensation, loss of muscle strength, loss of sweating, and enlarged and/or painful nerves (Table 16.1), although in the early phase of the disease, small fibre pathology is predominant. Though an enlarged nerve is one of the major criteria to diagnose leprosy, there are other conditions mimicking leprosy in this particular aspect (Table 16.2).

There are no reliable laboratory tests to diagnosis leprosy, let alone PNL. Complete skin and nerve examinations are mandatory, and electrophysiology [6–9] and biopsy may be of great help (Fig. 16.1, Table 16.3) [6, 7, 9]. In some instances, fine needle aspiration with polymerase chain reaction (PCR) may help to establish the diagnosis. The most common presentations of PNL are mononeuropathies and multiple mononeuropathies. When a neuropathy is established, history-taking becomes extremely important, since the aetiology can be diverse (Table 16.4). Careful neurophysiological evaluation may be of help. Some of the neuropathies including leprosy may be accompanied by neuritis. This is a general term for inflammation of peripheral

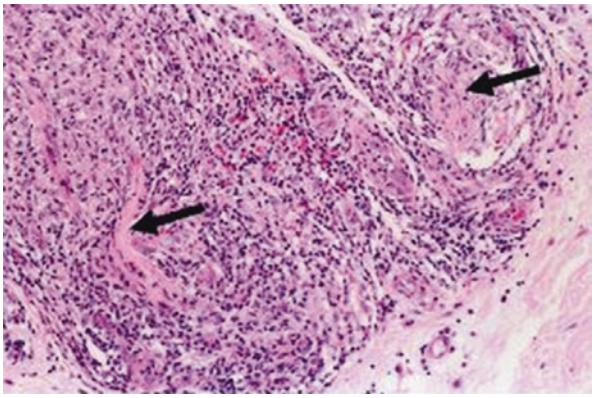

**Fig. 16.1** Tuberculoid granulomas compromising neural branch and neural fragments inside (arrows). Epithelial macrophages are surrounded by lymphocytes expanding and destroying neural structures (HEx20)

**Table 16.3** Histopathological spectrum of neural leprosy

- Tuberculoid pattern
- Borderline pattern
- Multibacillary pattern
- Multibacillary leprosy pattern with endoneural hyalinization/fibrosis
- Nonspecific oedema: nonspecific inflammatory endo- and perineural infiltrate (mycobacterial antigenic determinants present)
- Demyelination: nonspecific inflammatory infiltrate and demyelination (mycobacterial antigenic determinants present); complete demyelination, endo- and perineural hyalinization/fibrosis
- Nonspecific endoneural hyalinization/fibrosis
- No changes

**Table 16.4** Causes of peripheral neuropathy

- Systemic illness (diabetes, uraemia, sarcoidosis, myxoedema, acromegaly): polyneuropathy or multiple mononeuropathy
- Autoimmunity (inflammatory demyelinating polyradiculoneuropathies a.o Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy): polyneuropathy or polyradiculoneuropathy
- Vasculitis (connective tissue diseases): multiple mononeuropathy
- Infections [leprosy, diphtheria, Lyme disease, human immunodeficiency virus (HIV), herpes zoster]: multiple mononeuropathy or polyneuropathy
- Cancer (paraneoplastic neuropathy): polyneuropathy or neuronopathy
- Nerve tumours; neuroma and neurilemmoma
- Paraproteinemic neuropathies (myeloma, cryoglobulinemia, monoclonal gammopathy neuropathy of unknown significance): polyneuropathy
- Nutritional deficiencies and alcoholism: polyneuropathy, neuronopathy
- Compression, posture, and trauma: mononeuropathy
- Toxic industrial agents and drugs: polyneuropathy
- Hereditary sensory (and autonomic) neuropathies: polyneuropathy
- Hereditary motor and sensory neuropathies: and especially hereditary neuropathy with liability to pressure palsies (HNPP): polyneuropathy, polyneuronopathy
- Hereditary neuropathy with liability to pressure palsies (HNPP): mononeuropathy, multiple mononeuropathy, or polyneuropathy

nerves. The symptoms depend on the nerves involved, but may include pain, paraesthesia ("pins and needles"), hypoesthesia, anaesthesia, paresis, paralyses, and wasting of muscles. Nerve palpation may show tenderness, and a positive Tinel sign may be observed. When PNL is diagnosed, it must be treated. If the clinical and neurophysiologic pictures are those of a mononeuropathy, it might be considered as paucibacillary (PB). If they are of a multiple mononeuropathy, multibacillary (MB) leprosy must be diagnosed [7–9]. Since *M. leprae* is occasionally found in the nerve biopsy (Fig. 16.1), some consider that all PNL should be treated as MB. Moreover, some PNL patients develop skin lesions at a later stage [4], often during reactional episodes. However, some patients may show PNL having gone through a stage with skin lesions, which due to their harmless appearance have been missed.

PNL may be considered as a primary presentation of PB or MB leprosy. When a patient is diagnosed with mononeuropathy, multiple mononeuropathy, or even polyneuropathy, leprosy should always be among the differential diagnoses. Permanent nerve damage can be avoided when the patient is treated in a timely and adequate fashion.

## 16.3 Discussion

In 1977, Shetty and Antia published that nerves in early leprosy and in leprosy contacts showed signs of demyelination in nerve conduction studies and in histopathology [10]. Diogo Fernandes dos Santos presented during the Brazilian Leprosy Congress in 2017 that using nerve conduction studies demyelination in contacts was seen, with and without a positive anti PGL-1 serology [11]. During the Manila World Leprosy Congress in 2019, Glauber Voltan and Marco André Frade said they had found enlarged nerves in contacts using ultrasound (personal communication). The enlargement was related to the amount of exposure. In these studies, no clinical symptoms due to nerve dysfunction of the investigated nerves was demonstrated. It is generally assumed that clinical dysfunction only can be detected when more than 20% of the nerve fibres are not functioning. These observations, published on the Leprosy Mailing List in February 2020, raise the question of whether the abnormalities found can still be called leprosy, let alone PNL. There are no sensory or other clinical defects, but there are histopathological and nerve conduction abnormalities [12]. The only way to diagnose PNL may be when live *M. leprae* can be detected by fine needle aspiration using reverse PCR; otherwise, the damage could be due to contact with *M. leprae* antigenic determinants from the environment and it may be not a straight infectious disease.

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