Lepr Rev (2017) **88,** 274–279

CASE REPORT

Sensory mononeuritis: differentiating pure neural leprosy from non-systemic vasculitic neuropathy

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Accepted for publication 27 March 2017

Summary We describe two cases of sensory mononeuritis that presented with similar past medical histories, and clinical and electrophysiological features. The two patients were females who had resided in areas endemic for leprosy (Brazil). Both developed a progressive, purely sensory, painful mononeuritis distally in the lower limbs with sensory nerve potentials asymmetrically reduced in amplitude. The sural nerve biopsy performed in Patient 1 showed granulomatous inflammation of the epineurial tissue, consistent with paucibacillary pure neural leprosy (PNL) while in Patient 2 there were signs of vascular inflammation consistent with non-systemic vasculitic neuropathy (NSVN). Patients 1 and 2 both improved following targeted treatment with rifampicin and dapsone vs. rituximab, respectively.

Keywords: sensory painful mononeuritis, pure neural leprosy, vasculitic neuropathy, nerve biopsy

Introduction

Pure neuritic leprosy (PNL), a rare infectious neuritis treatable with antibiotics, accounts for about 4 to 8% of leprosy cases[1] yet the absence of skin lesions often leads to misdiagnosis. PNL occurs in any type of leprosy yet histopathological changes are compatible with borderline tuberculoid or lepromatous leprosy in most cases.[2] Neural involvement includes damage to nerve trunks and cutaneous nerve endings resulting in sensory and/or motor impairment. The earliest and most common disease forms are sensory with mainly

Patient consent: Oral and written informed consent was obtained from the two patients for publication of this paper and any accompanying images.

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 0305-7518/17/064053+06 $1.00

mononeuropathy (60%) followed by multiple mononeuropathy and polyneuropathy.[3] The commonest peripheral nerve trunk to be affected is the ulnar nerve (93·8%) followed by the lateral popliteal (62·5%) and radial cutaneous nerve (41·7%) and temperature and pain sensation are the first to be affected[4,5]

In a large case series of patients with histologically proven vasculitic neuropathy[6] almost half of the patients had non-systemic disease with restricted nerve and muscle involvement. This disorder, also rare, is treatable with immunosuppressive medication.[7] The neuropathy is reported as non-systemic vasculitic neuropathy or NSVN.[8] Clinical features are typically subacute yet some patients are symptomatic for many years prior to diagnosis. Symptoms include sensory or sensory-motor involvement, asymmetric pattern, and lower-limb predominance. Non-demyelinating electrodiagnostic features are a characteristic.[9]

Here, we report two cases of pure sensory mononeuritis, one as initial presentation of PNL and the other as the only manifestation of NSVN. Our aim is to show the diagnostic difficulty in two cases with similar past medical histories, clinical and electrophysiological features, and to underscore the usefulness of sural nerve biopsy as a confirmatory diagnostic tool.

Case Reports

PATIENT CHARACTERISTICS

The two female patients had no significant prior medical history and were not taking any medication. Family histories were negative for neurological disease. Both of them developed a progressive, asymmetric, purely sensory and painful mononeuritis distally in the lower limbs. Before symptom onset they had both resided in areas endemic for leprosy (Brazil) for 11 and 22 years respectively.

Patient 1, a 33 year-old hairdresser, initially complained of progressive painful tingling in the toes of the right foot, increased leg fatigability and bilateral heel pain. Four to 6 weeks later she reported progressive painful ankle edema, more pronounced on the right side. On neurological examination, no intrinsic foot muscle wasting or weakness was found however bilaterally reduced Achilles tendon reflexes and asymmetric sensory deficits were observed distally in the lower limbs including, on the right side, heel anesthesia, touch and pressure hyposensibility at the plantar and lateral foot parts and loss of vibratory sensation on the big toe; moreover, a pronounced painful ankle edema with nodular induration was palpated. On the left, dysesthesias on the dorsal foot surface were reported and slight lateral left ankle edema was observed. No areas of skin depigmentation or other skin changes were observed. The cervical plexus was not palpable.

Patient 2, a 51 year-old physician, initially reported a progressive burning and pricking pain and dysesthesias on the lateral part of both feet. Over the following weeks, symptoms spread across the whole feet, especially on the left side. They were worse in the evening disturbing sleep and were aggravated by mechanical constraints. On examination amyotrophy without weakness of extensor digitorum brevis muscles more pronounced on the left, reduced Achilles tendon reflexes and asymmetric sensory deficits with dysesthesias distally in both lower limbs were found. Moreover, reduced tactile sensation on the lateral part of both feet and on the dorsum of the left foot was seen; vibratory sensation and sense of toe positions were normal. No skin or sweat changes were observed; a slight bilateral cervical plexus hypertrophy was palpated.

NERVE CONDUCTION STUDIES (NCS)/ELECTROMYOGRAPHY (EMG)

NCS were performed at 11 and 14 months after symptom onset for both patients. Data (Table 1) demonstrate asymmetrical reduction in sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitude in both cases, with a decrease greater than 50% between the two sides, compatible with an axonal-type predominantly sensory, multifocal mononeuropathy.

LABORATORY TESTING

The extensive blood workup including hematological, renal, hepatic, endocrinological and metabolic functions, immunologic (ANA, ANCA, RF, ESR) and serologic (HCV, HIV, syphilis, and Lyme disease) screening, serum protein electrophoresis and immune electrophoresis were unremarkable. Thoraco-abdominal CT scan was normal in both patients. In patient 1, ultrasound examination revealed posterior tibial and sural nerve thickening on both sides. Bacterial PCR performed on ankle skin and sural nerve biopsy specimens was negative. Nasal mucosa sample analysis for mycobacterium leprae was also negative. Accessory salivary gland biopsy in patient 2 did not reveal inflammatory changes. Genetic analysis performed in the same patient showed no deletion in the PMP22 gene.

Sural nerve biopsy in patient 1 showed fibro-inflammatory thickening of the epineurium with multiple small granulomas, without necrosis or mycobacteria in the Ziehl special stain (Figure 1A) compatible with a diagnosis of PNL. In patient 2 fibrous thickening of the epineurium and vascular/perivascular lymphocytic inflammation were seen around small vessels (Figure 1B), suggestive of NSVN.

TREATMENT AND OUTCOME

Both patients improved following targeted treatment at 11 and 16 months respectively after symptom onset. Patient 1 was treated with a 6-month rifampicin (600 mg) and dapsone (100 mg) monthly and daily regimen, respectively. Daily prednisone doses of 20 mg were also given at the start for 20 days in anticipation of a reversal reaction. Add-on treatments included pregabaline and cold compress application. At the 3 months follow-up she reported reduction of painful dysesthesia. Furthermore, less pronounced ankle edema and nodular

Table 1. Nerve conduction studies

Nerve conduction studies	*normal*	Patient 1	Patient 2
Peroneal CMAP (right motor at the ankle) recording EDB	$> 2{\cdot}5\,mV$	10·7	1·3
Tibial CMAP (right motor at the ankle) recording AH	$> 2{\cdot}5\,mV$	0·3	10·7
Superficial peroneal SNAP (antidromic)			
Above lateral malleolus to ankle, Right	$> 7\,\mu V$	13·9	7·1
Left		0	5·9
Sural SNAP (orthodromic)			
Below lateral malleolus to lateral calf, Right	$> 5\,\mu V$	0	2
Left		0	0

EDB, extensor digitorum brevis; AH, abductor hallucis.

The asymmetrical reduction in sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitudes found in Patients 1 and 2 are shown. Nerve conduction velocities were within normal range.

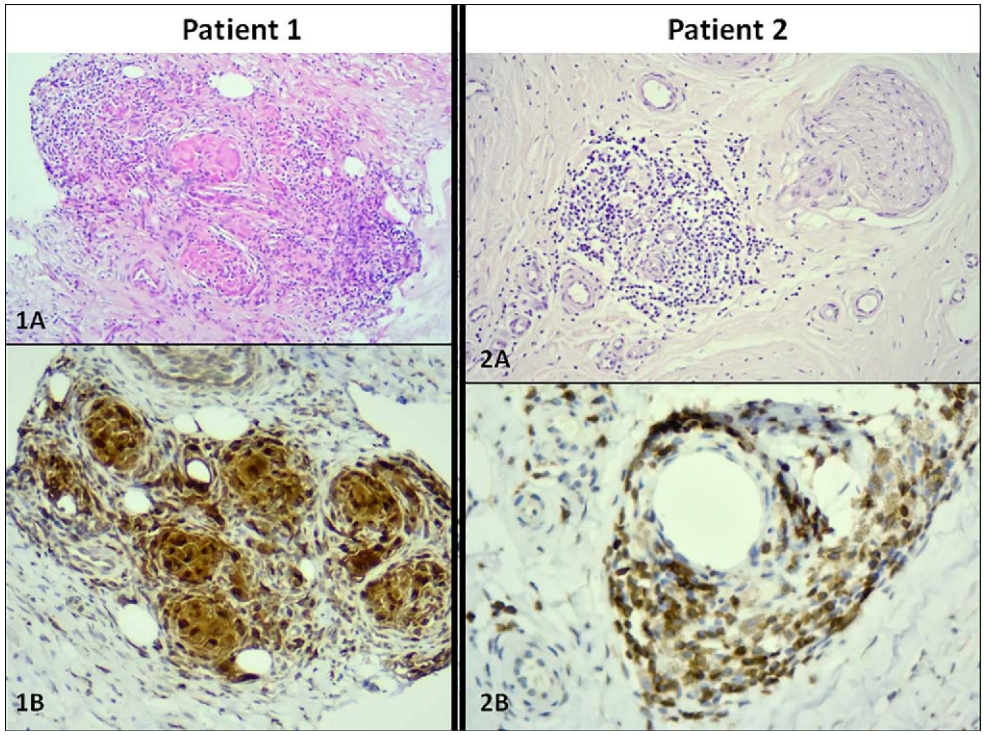

Figure 1. Nerve biopsies. Histology of Patient 1 is characterised by granulomatous inflammation in the epineurial tissue (1A: H&E staining, original magnification 100x), highlighted by immunostaining demonstrating macrophages (1B: CD68 immunostaining, original magnification 200x). Histology of Patient 2 is characterised by vascular/perivascular lymphocytic inflammation of small vessels in the epineurial tissue (2A: H&E staining, original magnification 100x), highlighted by immunostaining demonstrating T-lymphocytes (2B: CD3 immunostaining, original magnification 200x).

induration were found on the right side. A repeated NCS and examination remained unchanged. At the 24 month follow-up, less pain was reported yet the patient was unable to wear high-heeled shoes. Patient 2 received two infusions of 1 g of rituximab at 2 week intervals following the recently proposed vasculitis treatment recommendations.[9] Pregabaline was used with moderate pain reduction. At the $2\frac{1}{2}$ months follow-up after the second rituximab infusion, the patient reported symptom amelioration. Repeat NCS showed normal left sural SNAP and superficial peroneal bilaterally and; right sural SNAP remained absent. Given clinical stability and a slowly favorable outcome, no oral immunosuppressant agents were given. At the 24 months follow-up, progressive painful dysesthesia reduction was reported.

Discussion

This study was aimed at reporting rare causes of sensory mononeuritis. The interest of our two cases is their surprisingly homogeneous clinical and electrophysiological manifestations, including nerve hypertrophy. When a patient presents with one or more nodular-thickened nerves and patchy impairment of sensation, Hansen's disease should be suspected even if

there are no skin lesions.[10] These patients are easily misdiagnosed due to lack of skin involvement, the mean delay between symptom onset and leprosy diagnosis being approximately 2 years.[5] Notably, late appearance of edema and nodular induration in the vicinity of affected nerves as well as distinct pathological features with granulomas in nerve biopsy, were the cardinal features distinguishing our PNL and NSVN cases.

If epitheloid granulomas are seen in the peripheral nerve, leprosy should be considered in the differential diagnosis. Nerve biopsy is more informative and specific than skin biopsy in the diagnosis of leprosy.[11] Sensory and/or motor axonal neuropathy is the most common pattern seen in PNL prior to treatment.[5] It is of paramount importance that differential diagnosis of PNL and NSVN be considered when faced with sensory mononeuropathy cases in outpatient neurology or rheumatology settings especially in areas where leprosy is less common. Both our patients improved following disease-targeted therapy according to current treatment guidelines. Our study illustrates the diagnostic challenge of sensory mononeuritis when the signs and symptoms are purely neurological. Diagnosis should not be delayed or missed as this has significant therapeutic and prognostic consequences.

Abbreviations

PNL, pure neural leprosy
NSVN, non-systemic vasculitic neuropathy
NCS, nerve conduction studies
EMG, electromyography
SNAP, sensory nerve action potential
CMAP, compound muscle action potential
ANA, anti-nuclear antibody
ANCA, anti-neutrophil cytoplasmic antibody
RF, rheumatoid factor
ESR, erythrocyte sedimentation rate
HCV, hepatitis C virus
HIV, human immunodeficiency virus
CT, computed tomography
PCR, polymerase chain reaction

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