Nerve biopsy findings contribute to diagnosis of multiple mononeuropathy:
78% of findings support clinical diagnosis

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Abstract

Multiple mononeuropathy is an unusual form of peripheral neuropathy involving two or more nerve trunks. It is a syndrome with many different causes. We reviewed the clinical, electrophysiological and nerve biopsy findings of 14 patients who suffered from multiple mononeuropathy in our clinic between January 2009 and June 2013. Patients were diagnosed with vasculitic neuropathy ($n = 6$), perineuritis ($n = 2$), chronic inflammatory demyelinating polyradiculoneuropathy ($n = 2$) or Lewis-Sumner syndrome ($n = 1$) on the basis of clinical features, laboratory data, electrophysiological investigations and nerve biopsies. Two patients who were clinically diagnosed with vasculitic neuropathy and one patient who was clinically diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy were not confirmed by nerve biopsy. Nerve biopsies confirmed clinical diagnosis in 78.6% of the patients (11/14). Nerve biopsy pathological diagnosis is crucial to the etiological diagnosis of multiple mononeuropathy.

Key Words: nerve regeneration; peripheral nerve regeneration; multiple mononeuropathy; asymmetrical sensory-motor polyneuropathy; systemic vasculitic neuropathy; nonsystemic vasculitic neuropathy; perineuritis; inflammatory demyelinating polyradiculoneuropathy; Lewis-Sumner syndrome; sural nerve biopsy; skin biopsy; peripheral nervous system

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Introduction

Multiple mononeuropathy (MM) is an unusual form of peripheral neuropathy. MM is defined as a disorder involving two or more peripheral nerve trunks. Multiple nerves in random areas of the body can be affected. MM is a painful, asymmetrical, asynchronous sensory and motor peripheral neuropathy. As the condition worsens, it can be distributed bilaterally, distally and proximally throughout the body, and it becomes less multifocal and more symmetrical (Oh, 2001). The electrophysiologic diagnosis of MM requires side-to-side asymmetry (greater than 50%) for motor and sensory evoked potential amplitudes in two or more nerves. Conduction velocities need to be at least 75% of the lower limit of normal or no more than 25% above the upper limit of the normal range (Ross, 2012; Bromberg, 2013; Levine et al., 2013; Chung et al., 2014).

It is a syndrome associated with various underlying disorders, including vasculitic neuropathy (*e.g.*, systemic vasculitis, including Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis, and nonsystemic vasculitic disorder), primary Sjögren syndrome, IgM-related neuropathy, diabetes mellitus, infectious disease, perineuritis, granulomatous lesions (such as sarcoidosis), primary systemic amyloidosis, lymphoma and peripheral nerve tumors (Sim-

mons et al., 1992; Logigian et al., 1993; Kelkar et al., 2003; Ryan et al., 2003; Cattaneo et al., 2007; Sadek et al., 2010; Luigetti et al., 2013a, b; Koike et al., 2013; Teixeira et al., 2013; Tomita et al., 2013; Kara et al., 2014; Zhang et al., 2014).

The current literature consists primarily of clinical electrophysiological data, and most studies are case reports. In the current study, we investigate the clinical, electrophysiological and histopathological features of non-compressive and non-traumatic MM in Chinese patients.

Subjects and Methods

Subjects

Fourteen patients suffering from MM who underwent nerve biopsy in our clinic between January 2009 and June 2013 were included in the study. This work received approval from the Ethics Committee, Peking University Third Hospital, China.

Inclusion criteria: The patients had to be fully alert and able to give informed consent for the biopsy to be performed. Standardized neurological interviews and examinations were carried out on all patients by two professors of neurology prior to the biopsy.

Diagnostic criteria: All patients were classified based on their clinical features into one of three nerve lesion types:

mononeuropathy, MM and asymmetrical sensory-motor polyneuropathy. The diagnosis of mononeuropathy required that one of the peripheral nerve trunks was involved. Asymmetrical sensory-motor polyneuropathy (ASMN) refers to sensory-motor polyneuropathy, but with side-to-side asymmetry (Ross, 2012; Bromberg, 2013; Levine et al., 2013; Chung et al., 2014).

Methods

Electrophysiological examination

All tests were completed within 2 weeks of the patient's initial visit to our department for the study. All patients underwent electrophysiological tests, including the evaluation of motor and sensory conduction velocities in all four limbs. Nerve and muscle compound action potentials and nerve conduction velocity, and distal motor and F-wave latencies were measured according to previously described methods (Leis et al., 2011).

Nerve biopsy

Nerve biopsy was performed in an affected territory, which was the sural nerve at the ankle level in all patients. The nerve specimens (about 1–2 cm in length) were divided into two parts. One part was examined by light microscopy (Olympus BX41, Tokyo, Japan) after hematoxylin-eosin staining and immunohistochemistry. The EnVision two-step method was employed to examine nerve fibers and inflammatory markers. Neurofilament protein, peripheral myelin protein 22, myelin basic protein and S100 protein were labeled respectively with neurofilament protein (Dako, Carpinteria, CA, USA), peripheral myelin protein 22 (Sigma, St. Louis, MO, USA), myelin basic protein (ZSGB-BIO, China) and S100 (DAKO) antibodies. Inflammatory markers were labeled respectively with CD68 (Dako), CD3 (Dako), CD4 (ZSGB-BIO), CD8 (Dako), LCA (Dako) and HLA-DR (Dako) antibodies. Cells with brown granules in their nucleus or cytoplasm were considered positively stained. Different markers were used for different tissues and/or cell staining. The results were evaluated by two pathologists independently. The second part was examined by electron microscopy (Hitachi, Tokyo, Japan). Observation indices included the number of nerve fiber bundles, myelinated nerve fiber density, axonal degeneration, demyelination, perineurium thickness, vascular wall structure, and type and number of inflammatory cells.

Skin biopsy

Skin biopsy was performed in eight cases clinically suspected with vasculitic neuropathy for subsequent hematoxylin-eosin staining.

Laboratory examination

Routine blood tests, blood biochemical examination, serum immunological examination, serum tumor marker screening, cerebrospinal fluid (CSF) examination and other appropriate investigations were performed as needed to exclude other causes of neuropathy. Observation indices included CSF protein and/or cell abnormality, immune abnormality and serum tumor marker abnormality.

Results

Clinical manifestation

The clinical characteristics of 14 patients, 8 males and 6 females, is shown in **Table 1**. The mean age at the time of biopsy was 47.5 years (range: 18–77 years). The mean interval between the onset of symptoms and performance of the nerve biopsy was 17.8 months (range: 2–60 months). Two patients began with symptoms restricted to motor deficits, which later developed into sensory disturbance. Two patients had an initial presentation of motor deficits and sensory deficits. The other 10 patients had initial presentation restricted to sensory disturbance. Four patients complained of pain initially, and 13 patients suffered from pain during the disease. The most involved nerve was the ulnar nerve; eight patients had sensory deficits and/or motor deficits in the ulnar nerve as initial presentation. One patient (patient 12) had involvement of cranial nerves, with hearing impairment, diplopia and left ptosis. One patient (patient 13) had associated sensory ataxia. Six patients had systemic illness. Four patients had MM initially, but as the condition worsened, it became less multifocal and more symmetrical.

Vasculitic neuropathy

The most prominent finding was the high incidence of vasculitic neuropathy, which affected six patients. In this subgroup, necrotizing arteritis was demonstrated in two patients; one had a type 1 vasculitic lesion and the other had a type 2 vasculitic lesion. Histological signs of necrotizing arteritis (type 1) included segmental necrosis of the wall of epineurial and perineurial arteries, transmural inflammatory cell infiltration and occlusion of the lumen. Wallerian degeneration affected the majority of nerve fibers simultaneously, and larger myelinated fibers were more prone to axon loss (**Figure 1**). Histological signs of type 2 vasculitis included necrotizing arteritis, but without transmural inflammatory cell infiltration. In four patients, no necrotizing arteritis could be found, but the diagnosis of vasculitic neuropathy remained very likely because of the presence of inflammatory infiltrates in the vicinity of nerve vessels associated with axonal degeneration of nerve fibers and/or heterogeneity between each nerve fiber. Pathological diagnosis confirmed type 3 vasculitic lesion. Pathological typing of vasculitic lesions is detailed in the literature (Oh, 2001).

Of the six cases with vasculitic neuropathy, three patients (patients 1, 2 and 6) had systemic vasculitis (*i.e.*, systemic vasculitic neuropathy [SVN]), and three patients had vasculitis confined to the peripheral nervous system. Among the three cases of SVN, one (patient 1) had systemic lupus erythematosus (SLE), one (patient 2) had Sjögren's disease associated with rheumatoid arthritis, and one (patient 6) had antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The mean interval between the onset of symptoms and referral for biopsy was 40 months (range: 24–60 months). Three patients had MM as the pattern of nerve injury at onset. Two of these patients (patients 1 and 2) became less multifocal and more symmetrical, characteristic of ASMN, over time (2 months and 6 months later, respec-

Table 1 Clinical manifestation of 14 patients with MM

Patient	Gender/age (year)	Duration (month)	Neuropathy pattern (onset)	Neuropathy pattern (nerve biopsy)	Electrophysiology	Pathological diagnosis
1	M/75	24	MM	ASMN	Axonal ASMN	Type 3 vasculitic lesion
2	F/76	60	MM	ASMN	Mononeuropathy (right median nerve)	Type 1 vasculitic lesion
3	F/52	9	Mononeuropathy (right ulnar nerve)	MM	Normal	Type 3 vasculitic lesion
4	M/38	5	Monopathy (left ulnar nerve)	MM	MM (motor nerve: left axillary, musculocutaneous, peroneal nerves; sensory nerve: left median nerve)	Type 3 vasculitic lesion
5	F/77	24	MM	MM	Axonal ASMN	Type 3 vasculitic lesion
6	F/73	36	MM	MM	Axonal ASMN	Type 2 vasculitic lesion
7	M/21	2	MM	MM	MM (motor nerve: left median and right peroneal; sensory nerve: normal)	Perineuritis associated with perivasculitis
8	F/18	3	MM	MM	MM (motor nerve: bilateral ulnar, left peroneal and left tibial nerve; sensory nerve: normal)	Perineuritis
9	M/53	24	MM	MM	MM (motor nerve: left peroneal nerve; sensory nerve: bilateral sural and right median nerve)	Severe loss of myelinated fiber, myelin loose solution and demyelination in remaining myelinated fiber
10	M/34	2	MM	MM	MM (motor nerve: normal; sensory nerve: left ulnar and right sural nerve)	Mild demyelination
11	M/33	5	MM	ASMN	MM (motor nerve: normal; sensory nerve: right ulnar and right sural nerve;	Mild demyelination
12	F/47	4	MM	MM	Mulifocal demyelinating sensory-motor neuropathy	Some loss of myelinated fibre and few 'onion bulb' formation, slight perineurial macrophage infiltration
13	M/46	3	MM	ASMN	Demyelinating neuropathy	Some loss of myelinated fiber, demyelination and remyelination, and few 'onion bulb' formation
14	M/22	48	Monopathy (right ulnar nerve)	MM	Mutifocal demyelinating neuropathy associated with CBs in nonentrapment sites (motor nerve: bilateral ulnar nerves)	Mild demyelination

M: Male; F: female; MM: multiple mononeuropathy; ASMN: asymmetrical sensory-motor polyneuropathy.

tively). The other patient (patient 6) continued to have MM as the pattern of nerve injury over a period of 36 months. Electrophysiological investigation in this subgroup showed that two patients (patients 1 and 6) had axonal ASMN and one patient (patient 2) only had mononeuropathy. This highlights the inconsistency between the clinical features and electrophysiological characteristics; the electrophysiological abnormalities were asymmetrical in all three patients.

Three patients (patients 3, 4 and 5) had nonsystemic vasculitic neuropathy (NSVN). The mean interval between the onset of symptoms and referral for biopsy was 12.7 months (range: 5–24 months), shorter than that of SVN. Two patients (patients 3 and 4) had mononeuropathy as the pattern of nerve injury at onset, but progressed to MM over time (1 month and 0.5 months later, respectively). Electrophysiolog-

ical investigation was normal in patient 3, but pathology of the sural nerve was abnormal and showed inflammatory infiltrates in the vicinity of nerve vessels associated with mild axonal degeneration of nerve fibers. This finding indicates that pathological changes might precede electrophysiological changes (**Figure 2**).

Two patients (patients 9 and 10) were diagnosed with NSVN based on clinical, laboratory and electrophysiological findings. The nerve biopsies did not contribute to the diagnoses. Patients 7 and 8 had suspected NSVN based on clinical and electrophysiological findings. The pathological findings of sural nerve biopsy were consistent with perineuritis.

Perineuritis

The sural nerves of two patients (patients 7 and 8) demon-
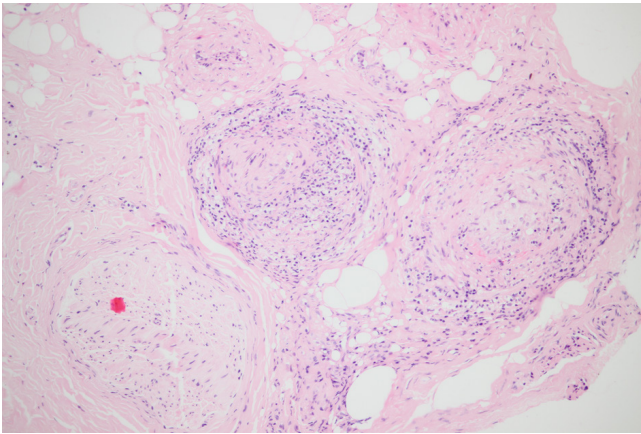
Figure 1 Biopsy result showing a type 1 vasculitic lesion (patient 2, female, 76 years old) (hematoxylin-eosin staining, × 100).
The walls of two perineurial arteries showed signs of necrosis, transmural inflammatory cell infiltration and occlusion of the lumen.
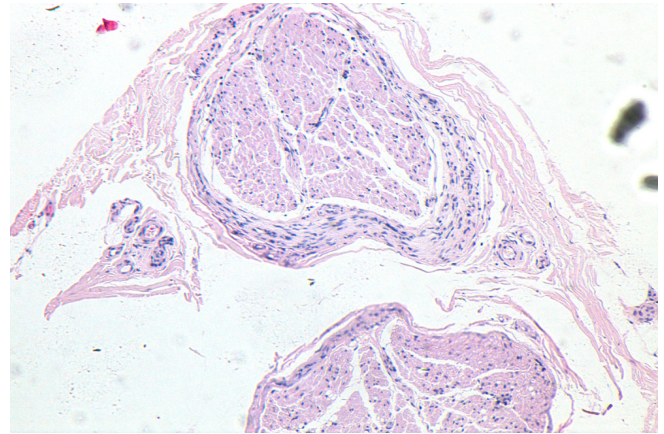
Figure 3 Biopsy results of an 18-year-old female patient with perineuritis (hematoxylin-eosin staining, × 100).
Sural nerve fascicle showed a thickened perineurium with infiltration of mononuclear cells .

Figure 4 Biopsy results of a 47-year-old female patient with chronic inflammatory demyelinating polyradiculoneuropathy (patient 12) (transmission electron microscopy, × 10,000).
A "onion bulb" formation is visible.
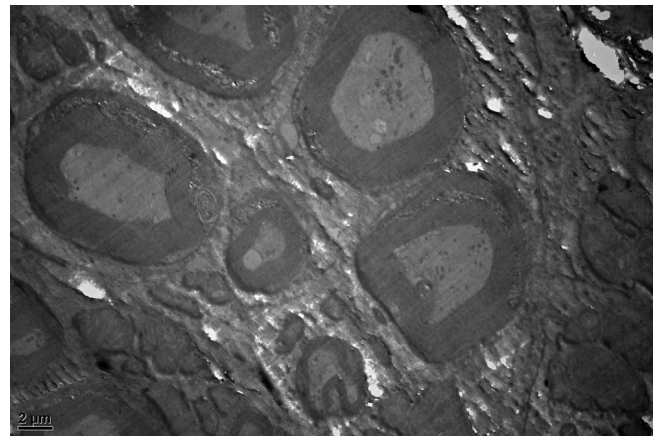
Figure 5 Biopsy results of a 22-year-old male patient with Lewis-Sumner syndrome (patient 14) (transmission electron microscopy, × 5,000).
The image shows mild demyelination.

Table 2 Clinical and pathological diagnosis

| Diagnosis	Number of cases	Contribution of nerve biopsy findings to the clinical diagnosis
Vasculitis neuropathy	8	6 definite; 2 not confirmed
Perineuritis	2	2 definite
CIDP	3	2 supported; 1 not confirmed
Lewis-Sumner syndrome	1	1 supported

CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy.

strated multifocal perineurial inflammation consisting mostly of mononuclear lymphocytes accompanied by histiocytes and perineurium thickened by collagen. This response was limited to the perineurium and did not involve the endoneurium (**Figure 3**). There was no evidence of necrotic vasculitis. Affected fascicles showed prominent axon loss, while others displayed axonal degeneration. Uninflamed fascicles showed mild axon loss. HLA-positive cells had infiltrated all fascicles, and had generally infiltrated the perineurium. Elec-

tron microscopy showed that the basement membrane of perineurial cells was thickened, that perineurial collagen was increased, and that perineurial cells had undergone degeneration. Patient 7 showed perivascular lymphocyte infiltration, and patient 8 had no vascular changes. These two patients were thus diagnosed with perineuritis based on pathological characteristics. Both patients were improved with methylprednisone and immune inhibitors.

The two patients had mononeuritis multiplex. Both had initial symptoms of numbness and pain, and then sensory and motor involvement. The mean interval between the onset of symptoms and referral for biopsy was 2.5 months (2 months and 3 months, respectively), shorter than that of SVN and NSVN. Neither of our patients had raised CSF protein. Electrophysiological investigation showed that compound motor action potentials (CMAPs) were remarkably reduced in several motor nerves. Sensory nerve conduction velocity of all examined nerves was normal in both patients.

Patient 7 had a swollen lymph node with good activity. B-mode ultrasonography showed a lymph node diameter of less than 1 cm with clear structure. Patient 8 had a past his-
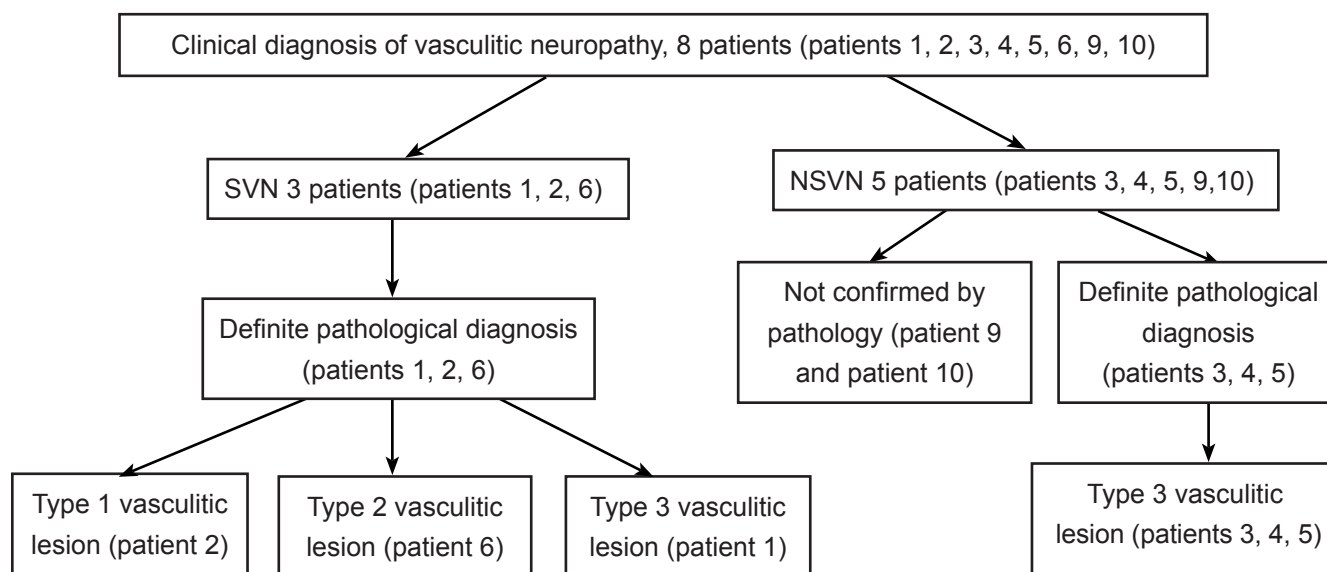
Figure 2 Flow chart showing the diagnostic procedure for vasculitic neuropathy.
SVN: Systemic vasculitic neuropathy; NSVN: nonsystemic vasculitic neuropathy.

tory of oral ulcer, but did not fit the criteria for diagnosis of Behcet's disease.

Chronic inflammatory polyradiculoneuropathy
Three patients (patients 11, 12 and 13) suffered from a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) based on clinical features and laboratory data. The mean interval between the first symptoms and the biopsy was 4 months (range: 3–5 months). All three patients in this subgroup had MM as the pattern of nerve injury at onset. Two of these patients (patients 11 and 13) developed ASMN over time (2 months and 0.5 months later, respectively). Patient 12 had involvement of the cranial nerves, and patient 13 had associated sensory ataxia. The CSF was abnormal with elevated CSF protein and normal CSF cell numbers in all three patients. All improved by intravenous administration of methylprednisone. Electrophysiological investigation in patients 12 and 13 showed multifocal demyelination. Morphological studies also showed some loss of myelinated fibers, a few "onion bulb" formations and a small amount of endoneurial inflammatory infiltration (**Figure 4**). There was slight perineurial macrophage infiltration in patient 12. In summary, these two patients were diagnosed with CIDP based on clinical features, laboratory data and electrophysiological characteristics. The nerve biopsies confirmed the clinical diagnoses.

Electrophysiological study of patient 11 showed that sensory nerve action potentials (SNAPs) were remarkably reduced in the right ulnar nerve and right sural nerve. CMAPs and motor nerve conduction velocity of all examined nerves were normal. Nerve biopsy showed mild demyelination. Therefore, patient 11 was diagnosed with CIDP based on clinical features and laboratory data, although the electrophysiological characteristics and nerve biopsy could not confirm the clinical diagnosis.

Lewis-Sumner syndrome
Patient 14 was diagnosed with Lewis-Sumner syndrome, *i.e.*, multifocal acquired demyelinating sensory and motor neuropathy. Patient 14 was a young man with initial symptoms of sensory and motor deficit in the bilateral ulnar nerves. After intravenous injection of immunoglobulins, symptoms soon improved, although there was still slight weakness in the right ulnar of two fingers. Six months later, he had numbness and pain in the left ulnar of two fingers and weakness in his right foot. The CSF was normal. Electrophysiology showed multifocal demyelination associated with conduction block in nonentrapment sites in the bilateral ulnar nerves. Mild demyelination was found on nerve biopsy (**Figure 5**). Genetic studies did not identify chromosome 17 mutations.

Results of skin biopsy
Skin biopsy was performed in 8 cases (patients 1, 2, 4, 5, 7–10) clinically suspected with vasculitic neuropathy. The presence of inflammatory infiltrates in the vicinity of dermis vessels was found in 3 patients (patients 1, 5 and 7), but no necrotizing arteritis was observed. There were no significant changes in skin biopsy among the other five patients. In this study, skin biopsy did not contribute to the final diagnoses.

Discussion
MM is an unusual form of peripheral neuropathy. Its global incidence is unknown because of the wide variety of underlying pathologies that may lead to the disorder. MM is actually a group of disorders, not a true distinct disease entity, and may be seen in association with a variety of systemic illnesses, as we report here. Our 14 patients were diagnosed as vasculitic neuropathy in six patients, perineuritis in two patients, CIDP in two patients, and Lewis-Sumner syndrome in one patient, based on clinical features, laboratory data,

electrophysiological investigations and nerve biopsies. Two patients were diagnosed with vasculitic neuropathy, and one patient was diagnosed with CIDP, based on clinical findings, but were not confirmed by nerve biopsy. Nerve biopsies confirmed or supported clinical diagnosis in 78.6% of the patients (**Table 2**).

MM mostly occurs in SVN and NSVN (Chalk et al., 1993). There are five clinical patterns of nerve injury in vasculitic neuropathy—mononeuropathy, MM, polyradiculoneuropathy, asymmetrical polyneuropathy and symmetrical polyneuropathy. A definite diagnosis of vasculitic neuropathy is dependent on nerve biopsy (Vital et al., 2006; Zivkovic et al., 2007).

MM is not the most common pattern in vasculitic neuropathy, being found in only about one-third of vasculitic neuropathy cases. Asymmetrical polyneuropathy or symmetrical polyneuropathy, especially axonal sensory-motor polyneuropathy, is the most common clinical pattern, being found in about half of cases (Oh, 2001; Vital et al., 2006).

Systemic vasculitic neuropathy has been reported associated with many systemic disorders, including primary systemic vasculitis neuropathy and secondary systemic vasculitis (Burns et al., 2007). However, nonsystemic peripheral nervous system vasculitis is not as well known. Some investigators consider NSVN a mild form of SVN with clinical involvement predominating in the peripheral nervous system. Supportive of this concept, many patients with NSVN exhibit subclinical vascular/perivascular inflammation in regional muscles and skin. Moreover, emerging evidence suggests that patients with NSVN are less likely to exhibit necrotizing vasculitis than those with SVN (Collins et al., 2009).

Our three patients (patients 3, 4 and 5) with NSVN had type 3 vasculitic lesions on sural nerve biopsy. Patient 3 had no muscle or skin biopsy performed. Patient 4 had no vascular/perivascular inflammation on skin biopsy. Patient 5 had mild perivascular inflammation on skin biopsy. All three patients should remain free of systemic involvement over a long period of follow-up.

Perineuritis as a unique clinicopathological entity was first described by Asbury in 1972. He reported two patients with a predominant sensory mononeuropathy multiplex (Asbury et al., 1972). Several reports of perineuritis with nerve biopsy findings subsequently appeared. Clinical presentations vary considerably, including mononeuritis multiplex, demyelinating neuropathy, distal sensory and motor neuropathy and polyradiculoneuropathy (Eric et al., 1997).

The diagnostic challenge presented by our patients was to determine the cause of sensorimotor mononeuropathy multiplex unaccompanied by evidence of an underlying systemic disease. Patient 8 had a history of oral ulcer, but no recurrent genital ulceration, eye lesion, skin lesion or other pathology. She was therefore not diagnosed with Behcet's disease (Saadoun et al., 2012). Patient 7 had a swollen lymph node with good activity. B-mode ultrasonography showed the diameter of the lymph node to be less than 1 cm with a clear structure. We consider this represents benign lymph node swelling, and will follow up our patient closely.

CIDP is a heterogeneous disorder, with a wide range of clinical expression, ranging from subacute to chronic progression, and a monophasic to a relapsing course. Additionally, it can include predominantly proximal to distal weakness, and may involve neuropathies ranging from symmetric polyneuropathy to mononeuropathy multiplex (Kuwabara et al., 2002).

Our three patients had MM as the pattern of nerve injury at onset. Two patients were diagnosed with CIDP on the basis of clinical features, laboratory data and electrophysiological characteristics. The nerve biopsies confirmed clinical diagnosis (Van den Bergh et al., 2010). Although not confirmed by nerve biopsy or electrophysiological studies, patient 11 was accepted as CIDP according to his clinical features, increased CSF protein and response to treatment. The nerve biopsy showed mild demyelination, and no vasculitis or axonal degeneration was present. Patient 11 was thus considered as an MM variant of CIDP.

Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy) is characterized by weakness and atrophy in the distribution of individual peripheral nerves with upper limb predominance. The predominant electrophysiological features are the presence of motor conduction block, contrasting with a mild degree of demyelination outside the blocked nerve territory. Sural nerve biopsies showed elements consistent with primary demyelination (Ryan et al., 2003; Viala et al., 2004). All of these findings were evident in patient 14.

In this study, vasculitis, perineuritis, CIDP and Lewis-Sumner syndrome were diagnosed based on clinical features, laboratory data, electrophysiological investigations and pathological testing of nerve biopsies. A detailed and complete medical history is vitally important in determining the possible underlying cause of MM. Recognition of early symptoms should be encouraged so that prompt treatment can be given.

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