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Clinicopathologic features of nonsystemic vasculitic neuropathy and microscopic polyangiitis-associated neuropathy: A comparative study

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Abstract

Objective: To compare clinicopathologic findings in nonsystemic vasculitic neuropathy (NSVN) and microscopic polyangiitis-associated neuropathy (MPAN).
Methods: Patients clinicopathologically confirmed to have NSVN ($n=23$) or MPAN ($n=40$) were compared with respect to clinical, electrophysiologic, and histopathologic features.
Results: Clinical features of neuropathy such as initial symptoms, progression, and distribution of sensory and motor deficits were similar in both groups, while functional compromise was greater in MPAN than NSVN. Abnormalities of laboratory data including those reflecting severity and extent of inflammation such as C-reactive protein were more conspicuous in MPAN than NSVN. Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were positive in two-thirds of patients with MPAN but negative in all NSVN. Electrophysiologic and histopathologic findings indicated axonal neuropathy in both groups, whereas the reduction of compound muscle action potentials in the tibial nerve and sensory nerve action potentials in the median nerve was significantly more profound in MPAN than NSVN. As for the epineurial perivascular infiltration, frequencies of cell-specific markers for T lymphocytes, macrophages, and B lymphocytes among cells infiltrating the vasculitic lesions were essentially similar between groups.
Conclusions: Clinicopathologic profiles and vascular pathology were similar between NSVN and MPAN but the age at onset, severity, and presence of p-ANCA were clearly different. Further study is needed to clarify the pathogenesis of NSVN and its place in the vasculitic spectrum of diseases.

Keywords: Nonsystemic vasculitic neuropathy; Microscopic polyangiitis; Sural nerve biopsy

1. Introduction

Vasculitic neuropathy occurs in association with various diseases including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, infection, malignant neoplasia, and cryogloblinemia [1]. In addition to vasculitic neuropathies secondarily to these diseases, primary systemic vasculitides including microscopic polyangiitis (MPA), Churg-Strauss syndrome, and Wegener's granulomatosis are known to involve the peripheral nervous system. Finally, vasculitis confined to the peripheral nervous system without systemic manifestations has been reported [2,3]. Subsequently, Dyck et al. described 20 patients with vasculitic neuropathy in the absence of other organ involvement [4]. These patients showed few laboratory abnormalities suggesting either systemic inflammation or collagen diseases, lacked nonspecific constitutional symptoms such as fever or weight loss, and had a favorable prognosis [4]. Since then, such vasculitic neuropathy has been known as nonsystemic vasculitic neuropathy (NSVN) and has attracted attention mainly among neurologists. Although NSVN possesses distinctive clinical features, involving only the peripheral nervous system, pathogenesis has remained unknown. In addition, vasculitis in this neuropathy has not been proven pathologically to be confined to the peripheral nervous system, so it might subclinically involve other organs. A related question is whether NSVN has a pathogenesis

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distinct from that of systemic vasculitides, especially MPA. MPA, a vasculitis involving small vessels including arterioles, venules, or capillaries [5], originally was considered a subtype of polyarteritis nodosa with rapidly progressive necrotizing glomerulonephritis and sometimes lung hemorrhage [6]; because of frequent renal involvement [5], this disorder has been studied by nephrologists as well as rheumatologists, with far less attention given to its neurologic aspects [5,7]. Since diagnostic criteria for primary vasculitis, such as those of Chapel Hill Consensus Conference [7], have been established mainly by rheumatologists, the nosologic relationship of systemic vasculitides to NSVN has remained obscure.

In this study we compared clinicopathologic features of neuropathy without and with systemic involvement (so-called NSVN and MPA-associated neuropathy: MPAN) to clarify the relationship of NSVN to systemic vasculitic neuropathy.

2. Patients and methods

2.1. Patients

Clinicopathologic findings in consecutive patients with pathologically confirmed NSVN and MPA-associated neuropathy (MPAN) with systemic involvement who were referred to Nagoya University Graduate School of Medicine and performed sural nerve biopsy from 1990 to 2003 were retrospectively compared. In the NSVN group symptoms of vasculitis were confined solely to the peripheral nerves, with no clinical or laboratory evidence of other organ involvement [4]. Laboratory data in this group were normal or only mildly abnormal, without indicating any other underlying disease. Inclusion criteria for the MPAN group were based on the classification proposed by the Chapel Hill Consensus Conference in 1994 [7]. In addition to peripheral nervous system, MPAN group was required to show signs of involvement of other organs such as lung or kidney, or a positive titer for perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) for inclusion [5,8]. Signs of a pulmonary-renal syndrome included acute renal insufficiency, hemoptysis, dyspnea, anemia, and alveolar shadowing on the chest radiograph [5]. Presence of vasculitis in the epineurium of sural nerve biopsy specimens was required for inclusion in either group. Vasculitis was defined as previously established [9]. Definite vasculitis was diagnosed if at least one blood vessel was infiltrated by inflammatory cells in association with signs of vascular injury such as fibrinoid necrosis, endothelial cell disruption, fragmentation of the internal elastic lamina, hemorrhage, or acute thrombosis. Probable vasculitis required transmural or perivascular inflammation unaccompanied by vascular destruction, but combined with at least one other supportive finding including vascular thickening, luminal obliteration, recanalized thrombus, epineurial neovascularisation, hemosiderin deposits, asymmetric nerve fiber loss, or ongoing Wallerian-like degeneration. Only subjects meeting criteria for definite or probable vasculitis were included in this study. Thus, patients with only perivascular inflammatory cell infiltration were not included. In the MPAN group 33 patients met definite criteria, while 7 met probable criteria. In the NSVN group, 11 patients met definite and 12 met probable criteria. Three patients for each group were clinically suspected as NSVN or MPAN but they did not fulfill the pathologic criteria. Patients with the other small-vessel angiitis such as Churg-Strauss syndrome, Wegener's granulomatosis, malignancy-associated vasculitis, or connective tissue disease-associated vasculitis were excluded. Based on these criteria, 23 patients with NSVN and 40 with MPAN were included.

The functional state of patients was estimated at the peak phase of neuropathy according to the modified Rankin scale [10]: 0, asymptomatic; 1, non-disabling symptoms not interfering with lifestyle; 2, mildly disabling symptoms leading to some restrictions of lifestyle but not interfering with capacity to look after oneself; 3, moderately disabling symptoms significantly interfering with lifestyle or precluding totally independent existence; 4, moderately severe disability precluding independent existence while not requiring constant attention around the clock; and 5, severe disability with total dependency requiring constant attention day and night.

2.2. Electrophysiologic assessment

Motor and sensory nerve conduction studies were performed in all patients before sural nerve biopsy was performed, using a standard method with surface stimulating and recording electrodes [11,12]. Motor conduction was investigated in the median and tibial nerves, with potentials recorded from the abductor pollicis brevis and abductor hallucis brevis muscles, respectively. Sensory conduction was investigated in the median and sural nerves, with potentials recorded at the second digit with ring electrodes and at the ankle, respectively.

2.3. Pathologic assessment of sural nerve specimens

Sural nerve biopsy was performed as described previously prior to initiation of therapy [13–15]. Specimens were divided into two portions. The first was fixed in 2.5% glutaraldehyde in 0.125 M cacodylate buffer (pH 7.4); then most of it was embedded in epoxy resin for morphometric and ultrastructural study. Density of myelinated fibers was assessed in toluidine blue-stained semithin sections using a computer-assisted image analyzer (Luzex FS; Nikon, Tokyo, Japan), and densities of small and large myelinated fibers were calculated as described previously [14–16]. A fraction of the glutaraldehyde-fixed sample was processed for teased-fiber study, in which at least 100 single fibers