Original Article

Vasculitic neuropathy in elderly: A study from a tertiary care university hospital in South India

Anish Lawrence, Madhu Nagappa, Anita Mahadevan[1], Arun B. Taly

Departments of Neurology and [1]Neuropathology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Abstract

Objective: To describe clinical, electrophysiological, and histopathological profile of vasculitic neuropathy in elderly subjects aged 65 years or more. **Design:** Retrospective chart review. **Setting:** Departments of Neurology and Neuropathology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India. **Patients and Methods:** Elderly subjects, diagnosed vasculitic neuropathy by nerve biopsy over one decade, were studied. **Results:** The cohort consisted of 46 subjects. Symptom duration was 21.54 ± 33.53 months. Onset was chronic in majority (82.6%). Key features included paresthesias (89%), weakness (80%), sensory loss (70%), wasting (63%), and relapsing-remitting course (6.5%). Most Common clinico-electrophysiological patterns were distal symmetrical sensorimotor polyneuropathy - 19, mononeuritis multiplex - 9, and asymmetric sensorimotor neuropathy - 10. Diagnosis of vasculitis was not suspected before biopsy in 31 (67.3%). Nerve biopsy revealed definite vasculitis - 12, probable - 10, and possible - 24. Treatment included immunomodulatory agents (41), symptomatic medications only (9), and antiretroviral therapy (1). Twenty-four patients were followed up for mean period of 6.5 months. Outcome at last follow-up was improved (13), unchanged (8), and worsened (3). **Conclusion:** Vasculitis is an important, treatable cause of neuropathy in elderly. Nerve biopsy should be used judiciously for early diagnosis and appropriate treatment.

Key Words

Elderly neuropathy, nerve biopsy, vasculitic neuropathy

For correspondence:
Dr. Arun B. Taly, Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru - 560 029, Karnataka, India.
E-mail: abtaly@yahoo.com

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Introduction

The elderly face a substantial amount of morbidity from neuropathic illnesses.[1] Management of neuropathy in elderly poses a great challenge to clinicians particularly with respect to the extent to which to investigate these patients to determine the etiology. This is in part due to the lack of comprehensive information about the clinicopathological patterns of neuropathy in the elderly. Although etiology can be established in many cases by a step-wise approach, a significant number of cases still remain undiagnosed.[2] Among the various etiologies of peripheral neuropathy, vasculitis is a potentially treatable entity, but establishing the diagnosis is fraught with many difficulties. Nerve biopsy is the "gold standard" test and isolated vasculitis of peripheral nervous system can be diagnosed only with a properly performed nerve biopsy.[3] Nerve biopsy is frequently delayed or avoided as it is an invasive procedure and vasculitis is often not suspected as the etiological cause of neuropathy in elderly. Elderly population also has a significant burden of systemic disorders that affect peripheral nerve vasculatures such as diabetes, hypertension, and peripheral occlusive vascular disease that poses difficulties in identifying the relative contribution of each of these diseases to neuropathy in a particular patient.[4] Vasculitis may coexist in a given individual with vascular risk factors. Very few studies have evaluated the role of nerve biopsy in the diagnosis of vasculitic neuropathy in elderly. In this study, we describe the clinical, electrophysiological, and histological findings in a cohort of elderly subjects with biopsy proven vasculitic neuropathy.

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Patients and Methods

Patient selection

This study was carried out at the Departments of Neurology and Neuropathology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India. Elderly subjects aged 65 years and above who underwent nerve biopsy between January 2002 and December 2011 were identified from the neuropathology archives. Subjects who had evidence of vasculitis on nerve biopsy were included in the study, and a retrospective chart analysis was carried out. The study was approved by the Institute Ethics Committee.

Details of clinical symptomatology, neurological deficits, and electrophysiological abnormalities were extracted from the case records. Family history of neurological disease, presence of comorbidities, and toxin exposure, if any, were noted. The progression of symptoms was classified as acute, subacute, or chronic when the duration of progression <4 weeks, 4–8 weeks, or >8 weeks, respectively. Results of laboratory investigations such as hemogram (including hemoglobin, total leukocyte count, and platelet count), erythrocyte sedimentation rate, biochemical parameters, serological tests, analysis of cerebrospinal fluid, neuroimaging, and other tests were recorded wherever available. Electrophysiological tests were carried out using standard protocols, and at least one motor and one sensory nerve each in the upper and lower limbs were examined.[5] A value beyond two standard deviation of the established laboratory control data were considered abnormal. The clinical and electrophysiological observations were used to categorize patients into symmetric or asymmetric, sensory or motor or sensorimotor polyneuropathy, multiple mononeuropathy, polyradiculoneuropathy, and mixed patterns. All medical case records were reviewed by two authors (AL and MN).

Nerve biopsies

Biopsy of sensory nerve found to be abnormal on nerve conduction study was carried out. The nerve biopsies were fixed in 2.5% glutaraldehyde, and one portion was processed for paraffin embedding. A second portion was prefixed in Fleming's solution and processed for Kulchitsky Pal stain for myelin. Longitudinal and transverse sections, 3 microns thick, were serially cut and stained with hematoxylin-eosin, Masson's Trichrome for collagen, and Kulchitsky Pal for myelin. In addition, periodic acid–Schiff, Congo red, and Perls Prussian Blue stain were carried out for detecting paraprotein/immunoglobulin, amyloid, and hemosiderin deposits, respectively. Immunohistochemistry by indirect immune peroxidase method was carried out in selected cases, using antibodies to leukocyte common antigen, monoclonal, 1:100, BioGenex, Fremont, CA, USA, to detect inflammatory infiltrates.

All nerve biopsy specimens were systematically reviewed by a single neuropathologist (AM) for the presence of subperineurial edema, myelinated fiber loss, acute myelin/axonal breakdown, demyelination, axonal regeneration, inflammatory cell infiltrate, and vascular alterations. The histopathological diagnosis was confirmed or revised based on the current established pathological criteria and correlated with treatment instituted to determine utility in clinical management. Biopsies were diagnosed as having "definite," "probable," and "possible" vasculitis in accordance with Collins criteria.[6]

- Definite vasculitis: Presence of transmural infiltration with or without fibrinoid necrosis
- Probable vasculitis: Presence of at least one vessel rimmed or infiltrated by inflammatory cells, in the absence of transmural infiltration; and the presence of other supportive pathologic features, namely either vascular alterations (vascular thickening and sclerosis, narrowing or obliteration of lumen, thrombosis with or without recanalization, epineurial capillary proliferation or neovascularization, and periadventitial hemosiderin deposits) or asymmetric nerve fiber loss/active wallerian-like degeneration.[6] In this study, inflammation was considered significant if ten or more epineurial inflammatory cells or five or more endoneurial inflammatory cells were present. A minimum of two vascular changes in the presence of inflammation and sectoral myelin loss was considered significant
- Possible vasculitis: Same as for probable vasculitis except for milder degree of inflammation is less than five cells in endoneurial and 5–9 cells in the epineurial compartment.

Data on treatment and outcome were gathered from the case records. The following parameters were noted: (i) Duration of follow-up, (ii) nature of immunosuppressant and route of administration, (iii) response to treatment, and (iv) clinical course and outcome at last follow-up. The data were entered into a Microsoft excel sheet for further analysis.

Results

Clinical profile

During the study period, 107 elderly subjects underwent nerve biopsy at our center. Seven patients were excluded from the study because of incomplete medical records and insufficient nerve biopsy material. Data of remaining 100 patients were analyzed. Prebiopsy diagnosis of vasculitic neuropathy was made in 22 subjects. Nerve biopsy showed "definite", "probable," and "possible" vasculitis in four, six, and five patients, respectively. In the rest, ischemic neuropathy ($n = 3$), Hansen's disease ($n = 1$), demyelinating neuropathy ($n = 1$), and chronic axonopathy ($n = 2$) were the diagnosis on nerve biopsy.

Nerve biopsy showed features of vasculitis in 46 patients. Based on Collins criteria, they could be classified into as definite in 12, probable in 10, and possible vasculitis in 24. The histopathological diagnosis in the remaining patients were ischemic neuropathy ($n = 18$), chronic axonopathy ($n = 18$), leprosy ($n = 10$), inflammatory demyelinating neuropathy ($n = 6$), and demyelinating neuropathy (without inflammation) ($n = 2$). The clinical, demographic details, and pattern of peripheral nerve involvement of these patients with biopsy proven vasculitic neuropathy are summarized in Table 1. Onset was in the lower limbs in the majority (42/46, 91.3%) and upper limb onset was noted in only four. The clinical course was chronic in 38 (82.6%), acute and subacute in four patients each. Majority of the patients had sensory symptoms in the form of paresthesias (89%) and impaired sensation (70%). Weakness was found in 80% and wasting in 63% of patients. In these

patients, the prebiopsy diagnoses included vasculitis (*n* = 15), diabetic neuropathy (*n* = 3), acute inflammatory demyelinating polyneuropathy (*n* = 3), chronic inflammatory demyelinating polyneuropathy (*n* = 3), paraneoplastic (*n* = 2), toxic (*n* = 2), Hansen's disease (*n* = 1), and nutritional deficiency (*n* = 1). In the remaining 16 patients, an etiological diagnosis could not be arrived at before nerve biopsy and were labeled as "undiagnosed" [Table 2].

The electrophysiological patterns of neuropathy in the order of frequency included symmetrical sensorimotor polyneuropathy - 19, asymmetrical sensorimotor polyneuropathy - 10, mononeuritis multiplex - 9, symmetric sensory neuropathy - 4, asymmetric sensory neuropathy - 1, symmetric motor neuropathy – 1, and lumbosacral plexopathy - 2. Serological test for HIV was carried out in 18 and was positive in one. Rheumatoid factor was positive in 5 out of 29 patients; antinuclear antibody (ANA) was positive in 4 out of 24; perinuclear antineutrophil cytoplasmic antibody (pANCA) was positive in 2 out of 15; and cytoplasmic ANCA (cANCA) was positive in 2 out of 16 patients in whom testing could be performed.

Treatment and outcome

Patients received with immunosuppressants based on financial feasibility and presence of other systemic comorbidities (*n* = 41). This included intravenous methyl prednisolone (*n* = 14), oral prednisolone (*n* = 10), intravenous cyclophosphamide (*n* = 9), azathioprine (*n* = 5), plasmapheresis (*n* = 4), methotrexate (*n* = 3), and intravenous immunoglobulin (*n* = 2). Additional treatment included antiretroviral therapy (*n* = 1) and symptomatic medications (*n* = 9). In five patients, no treatment was initiated due to lack of clinical review postbiopsy. Follow-up data were available for 24 patients. The mean duration of follow-up was 6.5 months. The outcome at the time of last follow-up was improved (*n* = 13), status quo (*n* = 8), and deteriorated (*n* = 3).

Discussion

Peripheral neuropathy is an important cause of disability in the elderly and includes many potentially treatable conditions such as vasculitic and inflammatory neuropathies.[7] Focused studies of neuropathy in elderly subjects aged >65 years that included histopathological observations have reported that vasculitic neuropathy accounts for 28–33% of all neuropathies.[8,9] The current study included elderly subjects who underwent nerve biopsy as a part of evaluation for neuropathy. The proportion of elderly subjects diagnosed vasculitic neuropathy based on nerve biopsy was higher in our study compared to other similar studies. This may be related to selection bias as the patients were chosen for biopsy based on the high index of suspicion by the clinician. The cost involved in evaluating elderly was specifically addressed in a recent study, where it was noted that magnetic resonance imaging and electrodiagnostic studies add to financial burden even in developed countries.[10] Nerve biopsy, though invasive, is relatively inexpensive and should be form a part of the diagnostic evaluation of peripheral neuropathy in elderly.

Second, our study revealed that a large proportion had symmetric sensorimotor neuropathy (39.1%) rather than asymmetric pattern or a mononeuritis multiplex that is expected in vasculitis.[11] Only four patients had ANA positivity, whereas two patients each showed pANCA and cANCA. Thus, vasculitis should be considered in the differential diagnosis of elderly subjects who present with symmetric length-dependent neuropathy notwithstanding the lack of clinical or laboratory features of systemic vasculitis. Given

Table 1: Clinical, demographic details and pattern of peripheral nerve involvement

Clinical Features	Observed Value
Male: female	2.8:1
Mean age at biopsy (years)	69.85±4.9
Mean duration of symptoms (months)	21.54±33.53
Onset	
Acute	4
Sub-acute	4
Chronic	38
Course	
Progressive	43
Relapsing-remitting	3
Systemic vasculitis	17
Diabetes mellitus	12/44
Clinical features	
Paresthesias	89% (35/39)
Weakness	80% (37/46)
Sensory loss	70% (28/40)
Wasting	63% (12/19)
Electrophysiology	
Axonal	33
Mixed demyelinating and axonal	10
Conduction blocks	3
Patterns of neuropathy	
Distal symmetrical sensorimotor polyneuropathy	18
Asymmetric sensorimotor neuropathy	10
Mononeuritis multiplex	9
Symmetrical sensory neuropathy	4
Others	5

Table 2: Correlation of pre- and post-biopsy diagnosis in elderly vasculitic neuropathy (*n*=46)

Prebiopsy diagnosis	Biopsy diagnosis			
	Definite vasculitis	Probable vasculitis	Possible vasculitis	Total
No prebiopsy diagnosis "undiagnosed" (*n*= 16)	5	2	9	16
Vasculitis (*n*= 15)	4	6	5	15
Diabetic neuropathy (*n*=3)	0	0	3	3
CIDP	1	0	2	3
GBS	0	1	2	3
Paraneoplastic	1	0	1	2
Toxic	1	1	0	2
Hansen's	0	0	1	1
Nutritional	0	0	1	1
Total	12	10	24	46

CIDP = Chronic inflammatory demyelinating polyneuropathy, GBS = Guillain-Barre syndrome

the difficulty in diagnosing nonsystemic vasculitis[3,12] and the potential therapeutic implications, nerve biopsy is indicated in all patients with neuropathy including those with "unknown" etiology.

Nerve biopsy helps in establishing the diagnosis of vasculitis. Nerve biopsy also distinguishes vasculitis from other causes of neuropathy. In our study, in 15 out of 22 subjects, a prebiopsy diagnosis of vasculitis was confirmed on biopsy. In the rest, nerve biopsy revealed other etiologies of neuropathy. Moreover, among the 46 subjects who were diagnosed vasculitic neuropathy, the diagnosis of vasculitis was not considered in 34 subjects before biopsy. Coexisting medical conditions and other factors resulted in missed diagnosis of vasculitic neuropathy before nerve biopsy. For instance, diabetes mellitus was seen in 27% (12 of 46). It is common to lump elderly subjects with clinical signs and symptoms of neuropathy as having "diabetic neuropathy." Likewise, the presence of toxic exposure, systemic malignancy, and vegetarian diet were the confounding factors that precluded the prebiopsy diagnosis of vasculitis. It is important to note that the presence of systemic comorbidities should not deter the clinician from looking for vasculitis as a cause for neuropathy. It is noteworthy that in one-third of patients (n = 16, 34.8%), no etiological diagnosis could be arrived at before nerve biopsy and were grouped as "undiagnosed etiology" before nerve biopsy established vasculitis as the underlying cause.

The response of vasculitic neuropathies to steroids and other immunotherapies is variable.[13] Treatment with combined steroids and cyclophosphamide is recommended based on retrospective studies.[13] Given the chronic nature of these neuropathies, even though the long-term outcome is reasonably good,[13] we experienced high dropout rates with follow-up data available only in 24 patients. The disease stabilized or improved in 21 patients (87.5%), which is marginally better than other reports.[14] Good outcomes were reported in vasculitic neuropathies across all age groups with adequate therapy in previous studies.[14,15] Our study reveals that good outcome can be expected even in the elderly population. However, this study is limited by the fact that treatment protocol and follow-up were not uniform in all patients, and we could not draw definite conclusions on the optimal nature, route, and duration of immunosuppressive therapy; focused studies in this direction are required. The study is also limited by its retrospective nature. Evaluation for underlying systemic vasculitis was not uniform.

Conclusion

Vasculitis is an important cause of neuropathy in the elderly. Nerve biopsy aids in diagnosis, especially in neuropathies of unknown etiology and should be performed irrespective of age and clinico-electrophysiological pattern of neuropathy. This has important implication for planning therapeutic strategies, particularly in the setting of elderly subjects with multiple comorbidities accounting for neuropathy.

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Conflicts of interest
There are no conflicts of interest.

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