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Ultrasonographic characteristics of peripheral nerves in primary systemic vasculitis: A cross-sectional study

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Abstract

Objective: To explore the ultrasonographic characteristics of peripheral nerves in primary systemic vasculitis (psV). *Methods:* Fifteen patients with psV, 36 with secondary systemic vasculitis (ssV) and 109 healthy controls (HC) were consecutively recruited. Nerve ultrasound was conducted to obtain cross-sectional area (CSA) at predetermined peripheral nerve sites and to detect hypervascularization. *Results:* Nerve enlargement was detected in all 15 psV patients, mainly distributing in a multifocal pattern. Compared to ssV patients, remarkable nerve enlargement was showed at M2-M5, M8-M10 segment of the median nerve, U2-U4 segment, U8 and U10 point of ulnar nerve, upper trunk, fibular nerve and sciatic nerve ($P < 0.05$) in psV patients. Hypervascularization was detected in 8 (53.33%) psV and 17 (47.22%) ssV patients, respectively.
Conclusion: Multifocal nerve enlargement was common in patients with psV. Compared to patients with ssV, nerve enlargement in psV patients presented in the more proximal segment with a higher degree, possibly due to the differences in disease duration. Hypervascularization was common in psV patients and might be related to an active inflammatory state of the peripheral nerve.

Keywords: Nerve ultrasound; vasculitis; observational studies

INTRODUCTION

The vasculitides comprise a heterogeneous spectrum of disorders involving different organs, including skin and nerve systems due to inflammatory destruction of vessel walls and focal ischemia.[1,2] Primary or secondary systemic vasculitis (psV or ssV) can be differentiated. The former can be further divided in antineutrophil cell antibodies (ANCA) associated vasculitides (AAV) including eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and non-ANCA associated vasculitides including polyarteritis nodosa (PAN), Kawasaki disease, giant cell arteritis and Takayasu arteritis.[3] The main causes of ssV include systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), and others.[4]

Peripheral nervous system (PNS) involvement in vasculitis syndromes is mainly seen in GP, MPA, and EGPA, and either presenting as a mononeuritis multiplex or asymmetric (axonal) neuropathy.[5] Besides, affection for brachial plexus and the cauda equina nerve root can also be seen in patients with psV.[6,7] All these may cause prolonged limb weakness or paresthesia in patients with vasculitis, significantly influencing their quality of life.

Currently, the diagnostic gold standard for vasculitic neuropathy consists of clinical examination, nerve conduction studies (NCS), and laboratory tests.[8] Structural changes in vasculitic neuropathy have been confirmed by several ultrasonographic studies using diverse ultrasound protocols and rating scales[9-15], which are reported to have a complementary effect to NCS in detecting peripheral neuropathy.[16] However, there is considerable heterogeneity in the patient characteristics, including the type of vasculitis within these studies. The clinical utility of magnetic resonance imaging (MRI) in vasculitis neuropathy remains unclear, the feasibility has been explored, but no clear added value has been presented beyond routine ancillary tests.[17,18] Due to the ease of operation and cost-effectiveness, high-resolution nerve ultrasound (HRUS) has been

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widely applied in diagnosing peripheral nerve damage in inherited and acquired neuropathies.[19-22] However, ultrasonographic studies on psV are scarce, most of which are case reports or target on single nerve.[9,10]

In this study, we aim to explore the usefulness of HRUS in detecting nerve involvement in patients with psV. We assessed multiple sonographic parameters for each patient and compare them with patients with ssV and healthy controls (HC). We hope to facilitate the application of nerve ultrasound and provide new insights for future studies in psV through the survey.

METHODS

Study population

Fifteen consecutive patients with psV were enrolled at the inpatient ward or outpatient clinic of the Department of Neurology, Peking Union Medical College Hospital (PUMCH), between July 2022 and July 2023. The inclusion criterion was based on the 2022 American College of Rheumatology/European Alliance of Associations (ACR/EAA) classification criteria[23], and all patients fulfilling the criteria of systemic vasculitis were included. We also enrolled 36 disease controls with ssV (32 SLE and 4 pSS) and 109 HC for comparisons. Results of HC have been reported in previous studies[24,25], and results of SLE would be presented in our unpublished study. Subjects with entrapment and traumatic peripheral neuropathy, diabetes, hyperthyroidism, alcoholism, malignancies, and other systemic diseases that might cause peripheral neuropathy were excluded.

The local medical ethical committee (PUMCH) approved the study protocol (JS1210). Written and informed consent was obtained from all participants.

Clinical and ancillary assessment

We evaluated patients with a predetermined set of clinical and ancillary investigations. For each patient, we collected the following information: (1) General information (name, gender, height, weight, contact information, disease duration, and clinical symptoms). The total disease duration was the time from disease onset to enrollment in months. (2) Detailed neurological examinations, mainly including muscle strength of bilateral shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, finger flexion, finger extension, thumb abduction, little finger abduction, hip flexion, knee flexion, knee extension, ankle dorsal flexion, ankle plantar flexion, toe dorsal flexion, and toe plantar flexion using the Medical Research Council (MRC) score, tendon reflex and sensory examination. The total MRC score was 160. (3) Results of ancillary examinations including ANCA (within the past three months), the level of inflammatory factors and immunoglobulin (within the past three days), and nerve conduction studies (NCS). NCS were performed according to basic principles by experienced electromyographers on a keypoint system with a Nicolet EMG machine (CareFusion, Middleton, Wisconsin).[26] The room temperature was maintained to ensure the patients' skin temperature remained above 31°C. Technicians were blinded to patient information. A decreased or absent distal compound muscle action potentials (CMAP), sensory nerve action potentials (SNAP), nerve conduction velocities, or prolonged distal motor latency according to the data from healthy individuals in our neurophysiology laboratory was considered electrodiagnostic proof of nerve involvement. Significant decreased CMAP or SNAP with relatively preserved nerve conduction velocities was considered axonal damage. (4) Treatment in three months before enrollment. At baseline, the Birmingham Vasculitis Activity score (BVAS) was used to measure the disease activity of psV[27] and the INCAT (Inflammatory Neuropathy Cause and Treatment) disability score was used to assess the activity limitation of included patients.[28]

Ultrasound studies

A Philips iU22 (Philips Medical Instruments, Bothell, WA) with a 5-17 MHz linear array transducer was deployed to evaluate the peripheral nerves. Except for depth, the initial settings were kept constant during all examinations. The transducer was adjusted perpendicular to the nerve to obtain the minimal cross-sectional image.

The cross-sectional area (CSA) at the predetermined sites of each nerve was measured by tracing just inside the hyperechoic rim of the nerve. In the study, the median nerve, ulnar nerve, cervical fifth to seventh (C5-C7) roots, brachial plexus, vagus nerve, tibial nerve, fibular nerve, sciatic nerve and sural nerve were measured bilaterally at predetermined sites in all subjects[24,25] (Supplementary Figure 1). The upper limit of the CSA for each nerve location was defined as the 95th percentile in HC, and we determined that the nerve was enlarged when the maximum

CSA was larger than the upper limit. The degree of enlargement was classified into three groups based on the ratio of the CSA of the nerve and relevant upper limit: mild enlargement 1.00-1.25 times; moderate enlargement 1.25-1.50 times; marked enlargement >1.50 times.

CSA of the largest fascicle was measured in the median nerve inside the hyperechoic rim of the fascicles (corresponding to the measurement of the CSA).[29] Enlargement of fascicle was defined by singular fascicle area larger than 95th percentile values of in HC.

Power Doppler was deployed to screen for increased nerve vascularization in the M4-5 and M8-9 segments of median nerves. The probe was gently placed on the skin, perpendicular to the median nerve for each point and the observation time was 10 seconds. The normal vascularization of nerves cannot be visualized with contemporary ultrasound machines; therefore any presence of vascularization on power Doppler was considered abnormal or increased vascularization.[11]

Sonoelastographic images were obtained by gently placing the probe on the skin at the 4-5cm above the elbow of each subject, perpendicular to the median nerve, avoiding additional manual compression. The elastogram appeared within a rectangular region of interest as translucent color-coded, real-time images superimposed on the B-mode image. The color-code represented the relative stiffness levels of the various tissues within the region of interest (a circular area with a diameter of 2mm). Red indicated soft, blue indicated hard and green and yellow indicated medium elasticity, as mentioned by Paluch *et al*.[30] The strain indicator on the monitor specified whether the displacement was sufficient to obtain local mean stiffness within the region of interest. For each point, the measure of stiffness would be repeated three times to get the final mean results (expressed in kilopascals, kPa).

Blinded to the NCS and independent from the authors diagnosing primary systemic vasculitis, one of the authors performed the sonographic examinations and successively a senior author rated all sonographic measurements.

Statistical analysis

The Shapiro-Wilk test was used to assess whether data exhibited a normal distribution. Normally distributed variables including age were expressed as means (standard deviation, SD) while non-normally distributed variables including weight and height were expressed as medians (range). The Mann-Whitney U-test was used to compare the mean CSA of each peripheral nerve, the largest fascicle, and nerve stiffness between vasculitic patients and HC. Independent-sample t test or Chi test was used to compare clinical variables, ancillary results, BVAS score, and INCAT score. Two-sided P-values were calculated for all analyses, and a $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS, version 23.0.

RESULTS

Clinical characteristics of included subjects

A total of 15 patients with psV [age (mean±SD, 52.87±14.37 years; range, 26-74 years); 8 male and 7 female], 36 patients with ssV [age (mean±SD, 42.75±15.43 years; range, 14-76 years); all female] and 109 HC [age (mean±SD, 41.71±15.86 years; range, 16-70 years); 57 male and 52 female] were finally recruited. Among them, psV patients included three patients with eosinophilic granulomatosis with EGPA, 3 with GPA, 7 with MPA, and 2 with PAN. The clinical characteristics of the involved subjects were provided in Table 1. The mean age of psV patients was significantly higher than that of HC ($P < 0.001$). There was no significant difference in gender ratio, height or weight between psV patients and HC.

Thirteen psV patients reported limb numbness or weakness at recruitment. All 15 patients were undergoing glucocorticoid therapy; and six of them were taking cyclophosphamide (CTX), five of them were receiving regular treatment with rituximab.

Nerve enlargement in vasculitic patients

Comparisons in CSA at different sites of peripheral nerves between vasculitic patients and HC were presented in Table 2 and Figure 1. Compared to HC, there was significant enlargement at the M1-M2 segment, M6 point and M8-M10 segment of the median nerve, U1-U4 segment and U6-U10 segment of ulnar nerve, upper trunk, vagus nerve, T2 point of the tibial nerve, F2 point of fibular nerve and S1 point of the sciatic nerve ($P < 0.05$) among psV patients. When compared to ssV patients, remarkable differences existed at the M2-M5 segment, M8-M10 segment of median nerve, U2-U4 segment and U8 and U10 point of ulnar nerve, upper trunk, fibular nerve and sciatic nerve ($P < 0.05$) in psV patients. (Supplementary Figure 2)

Table 1: Clinical characteristics of included patients and healthy controls

	psV	ssV	HC	Comparisons between psV and HC
N	15	36	109	
Composition	3 EGPA; 3 GPA; 7 MPA; 2 PAN	32 SLE; 4 pSS		
Age (years old)	52.87±14.37	42.75±15.43	41.71±15.86	***P*<0.001**
Gender (M/F)	8/7	36/0	57/52	*P*=0.644
Height (cm)	166.82±8.54	161.67±4.98	167.32±8.24	*P*=0.746
Weight (kg)	63.20±14.38	58.00±9.73	65.45±11.12	*P*=0.316
Total disease duration (months)	33.53±51.14	84.47±83.89		
Total treatment duration (months)	11.12±10.87	58.65±12.97		
Total MRC score	137.00±36.87	153.33±21.01		
Baseline INCAT disability score	3.40±3.00			
BVAS score	16 (1-22)			

Abbreviations: BVAS Birmingham Vasculitis Activity; EGPA eosinophilic granulomatosis with polyangiitis; F female; HC healthy controls; GPA granulomatosis with polyangiitis; INCAT Inflammatory Neuropathy Cause and Treatment; M male; MPA microscopic polyangiitis; MRC medical research council; psV primary systematic vasculitis; SLE systemic lupus erythematosus; PAN polyarteritis nodosa; pSS primary Sjogren's syndrome; ssV secondary systematic vasculitis.
Note: Normally distributed variables were expressed as means (standard deviation, SD) while non-normally distributed variables were expressed as medians (range).
P<0.05 was considered as significance, which was bold.

Based on upper limit from the data of HC, we further analyzed the distribution form of nerve enlargement in psV patients. As showed in Figure 2, nerve enlargement was identified in 255/960 (26.56%) points of all 15 patients, affecting 23 median nerves, 28 ulnar nerves, 15 brachial plexuses, 1 vagus nerve, 7 tibial nerves, 8 fibular nerves, 6 sciatic nerves, respectively. There were 7 patients and 6 patients showing moderate and marked nerve enlargement, mainly in the median and ulnar nerves. For the median nerve, the distribution of nerve thickening was relatively uniform, while for the ulnar nerve, nerve enlargement mainly showed in the arm segment (U6-U10). Enlargement in the fibular nerve at the proximal point accounted for one-third of the thickened points of the peripheral nerves in lower limbs.

Relationship between nerve enlargement and clinical factors in patients with primary systemic vasculitis

NCS were conducted in 12 of included psV patients, involving 89 peripheral nerves. Among them, 54 (60.67%) nerves reported axonal damage, in the form of mononeuritis multiplex or polyneuropathy. We analyzed the consistency between nerve ultrasound and NCS in detecting nerve damage based on median, ulnar, tibial, fibular and sural nerve results. As shown in Figure 3, 67 (44.67%) nerves were presenting enlargement among 150 tested nerves, and 18 (26.87%) were detected anomalies in NCS. Besides, 20 nerves were showing normal results both in NCS and nerve ultrasound. The overall consistency between nerve ultrasound and NCS was 40.43%.

Due to the limited number of patients with marked nerve enlargement, we further analyzed the potential risk factors of moderate or marked nerve enlargement in psV patients. As shown in Table 3, we found no significant difference in any of the included indicators between patients with and without moderate or marked nerve enlargement. We further compared the frequency of nerve enlargement in patients with different disease courses of peripheral nerve involvement. The results showed that nerve enlargement was shared in various stages of peripheral nerve involvement, while marked nerve thickening was significantly more common among patients with emerging limb weakness or numbness in the past 12 months (P =0.032) (Figure 4).

Other ultrasonographic indicators

Comparisons in the largest fascicle of the median

Table 2: Cross-sectional area (mm^2) at different sites of peripheral nerves in vasculitic patients and healthy controls

Nerve location	psV		ssV		HC		
	Mean±SD	Range	Mean±SD	Comparisons	Mean±SD	Comparisons	Upper limit (the 95th percentile)
Median nerve							
M1	7.50±2.71	3.61-17.00	6.58±1.60	0.124	6.60±1.32	**0.046**	8.00
M2	7.32±1.50	3.43-12.00	5.78±1.43	**<0.001**	6.56±1.14	**0.002**	8.00
M3	6.48±1.48	3.23-10.00	5.51±1.12	**0.002**	6.50±1.02	0.615	8.00
M4	6.63±2.45	3.26-13.90	5.44±1.17	**0.049**	5.97±0.91	0.875	7.00
M5	6.92±2.24	2.91-10.20	5.49±1.22	**0.036**	5.64±0.89	0.113	7.00
M6	6.92±2.24	3.00-15.00	6.12±1.53	0.090	5.76±0.94	**0.002**	7.00
M7	8.28±2.72	4.35-16.40	7.35±1.75	0.189	8.48±1.35	0.052	11.00
M8	9.40±2.66	4.33-16.10	6.99±1.56	**<0.001**	7.97±1.23	**0.004**	10.00
M9	8.83±2.07	4.27-13.00	7.49±1.65	**0.006**	7.91±1.20	**0.023**	10.00
M10	9.01±1.61	4.10-13.40	7.60±1.76	**<0.001**	7.80±1.24	**<0.001**	10.00
Largest fascicle	0.91±0.31	0.04-2.00	0.70±0.24	**<0.001**	0.34±0.15	**<0.001**	0.60
Ulnar nerve							
U1	3.54±1.26	2.00-8.00	3.47±0.86	0.755	2.97±0.59	**0.010**	4.00
U2	4.61±1.05	2.00-7.03	3.74±0.87	**<0.001**	3.97±0.84	**0.002**	5.00
U3	5.25±1.39	2.18-9.00	4.24±1.29	**<0.001**	4.59±0.82	**0.005**	6.00
U4	5.34±1.24	2.16-8.92	4.52±1.06	**0.001**	4.53±0.82	**<0.001**	6.00
U5	5.47±1.81	2.59-10.00	4.97±1.38	0.280	4.90±0.89	0.340	6.00
U6	7.40±1.81	2.93-13.00	6.71±1.97	0.055	5.74±1.23	**<0.001**	7.00
U7	6.19±2.02	2.57-12.00	5.47±1.50	0.110	4.91±0.88	**<0.001**	6.00
U8	6.94±2.36	3.00-14.20	5.52±1.45	**0.002**	4.42±0.82	**<0.001**	6.00
U9	6.04±1.33	2.00-11.00	5.58±1.52	0.054	4.49±0.90	**<0.001**	6.00
U10	6.47±1.72	3.00-10.30	5.60±1.44	**0.017**	4.50±0.92	**<0.001**	6.00
Brachial plexus							
C5 root	5.66±1.71	3.00-14.70	5.89±1.76	0.528	5.33±1.32	0.230	7.00
C6 root	7.91±2.04	3.88-20.20	8.49±2.64	0.441	8.06±1.36	0.951	10.00
C7 root	8.49±2.64	4.08-14.20	8.30±1.90	0.221	8.50±1.23	0.310	10.00
Upper trunk	15.11±3.55	5.00-26.00	13.27±3.00	**0.010**	13.08±3.34	**0.003**	18.00
Middle trunk	10.21±3.51	4.00-17.80	10.11±2.07	0.597	9.28±1.41	0.458	12.00
Vagus nerve	1.29±0.43	0.75-3.26	1.43±0.48	0.133	1.14±0.35	**<0.001**	2.00

Tibial nerve							
T1	10.46±2.98	4.70-17.40	9.74±2.54	0.223	10.28±1.83	0.705	14.00
T2	22.50±5.06	5.86-45.00	21.34±5.77	0.147	20.84±3.50	**0.049**	27.00
Fibular Nerve							
F1	8.20±2.23	4.00-17.40	6.80±1.76	**<0.001**	9.56±1.95	**<0.001**	13.00
F2	9.48±2.31	4.00-23.90	8.32±3.13	**0.003**	8.40±1.83	**0.023**	11.00
Sciatic nerve							
S1	40.35±6.11	9.00-56.00	34.36±6.66	**<0.001**	33.12±6.40	**<0.001**	45.00
Sural nerve							
Su1	2.27±0.42	1.00-4.00	2.22±0.50	0.571	2.11±0.49	**0.003**	3.00

Abbreviations: HC healthy controls; psV primary systematic vasculitis; SD standard deviation; ssV secondary systematic vasculitis.
Note: Mann-Whitney U test was used for comparison of cross-sectional areas between vasculitic patients and healthy controls. $P \leq 0.05$ was considered as significance, which was bold.

nerve indicated significant enlargement of the fascicle in patients with psV than HC ($P<0.001$). Based on the upper limit of HC, fascicle enlargement was identified in 24/30 (80.00%) of tested median nerves in 12 psV patients. Among them, 7 nerves showed axonal damage in NCS.

Comparisons in nerve stiffness of median nerve suggested no significant difference between psV patients and HC (mean±SD, 21.37±6.41 vs 20.08±4.59 kPa, $P=0.330$).

Presence of vascularization was detected in 9/30 (30.00%) of tested median nerves in 8 psV patients. Further analysis showed that patients with increased intraneural vascular flow experienced shorter disease duration ($P=0.479$), had a higher positive rate of ANCA ($P=0.189$), higher level of BVAS ($P=0.275$) and INCAT disability score ($P=0.532$), although there was no significant difference. Besides, the serological level of IgG ($P=0.019$) and IgA ($P=0.048$) was significantly lower in psV patients with the presence of vascularization than those without. (Supplementary Table 1). For ssV patients, hypervascularization was detected in 23/72 (31.94%) median nerves among 17 included subjects.

DISCUSSION

Vasculitic neuropathy, characterized by an acute or subacute and painful onset of sensory and motor deficits of multiple nerves, was one of the main manifestations of patients with systemic vasculitis.[31-33] In the study, we systemically explore the characteristics of structural changes in peripheral nerves through HRUS among vasculitic patients.

Our results suggested the frequent occurrence of nerve thickening in psV patients in the form of multifocal distribution, corresponding to the underlying inflammatory mechanism.[34] The enlargement mainly focused on the peripheral nerves in the upper limbs, especially in arm segments of the median and ulnar nerves, with a lower incidence in the brachial plexus, cervical nerve roots, and lower limbs. Consistent with our results, Goedee *et al*. reported the low detection rate of thickening in the brachial plexus, which might reflect its relatively high endoneurial capillary density and thus, a potentially higher resistance to ischemic injury.[11] However, it was reported that nerve enlargement was prone to be seen at common sites of nerve compression (i.e., cubital sulcus, carpal tunnel, and fibular head) in patients with vasculitic neuropathy[11] and in lower limbs.[2] Besides, Üçeyler *et al*. suggested that superficial peroneal nerve enlargement might

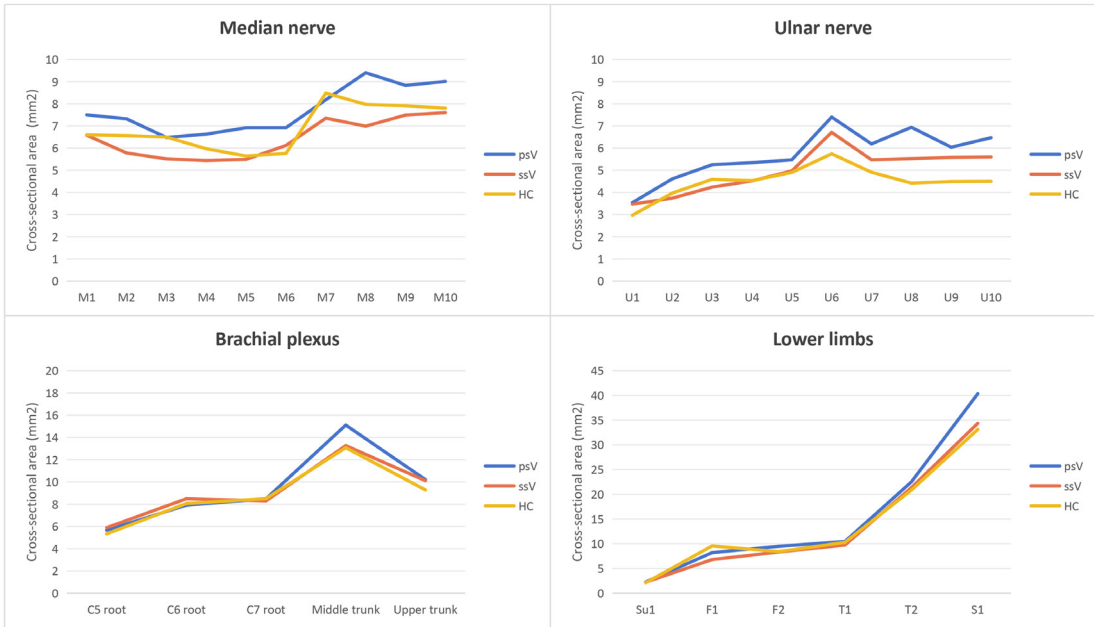

Figure 1. Comparisons in mean cross-sectional area (mm^2) of each site of nerves between vasculitic patients and healthy controls. psV primary systematic vasculitis; ssV secondary systematic vasculitis: HC healthy controls.

be a helpful parameter indicating vasculitic neuropathies.[14] Our study did not reach these conclusions, possibly due to the high heterogeneity in CSA of peripheral nerves in lower limbs[25] and differences in measurement sites.

Compared to patients with SLE or pSS, the segment of nerve enlargement was relatively proximal in patients with psV. Besides, the CSA of peripheral nerves at multiple sites was significantly higher in psV than those in SLE or pSS while remarkably smaller than those in demyelinating polyneuropathy including chronic inflammatory demyelinating

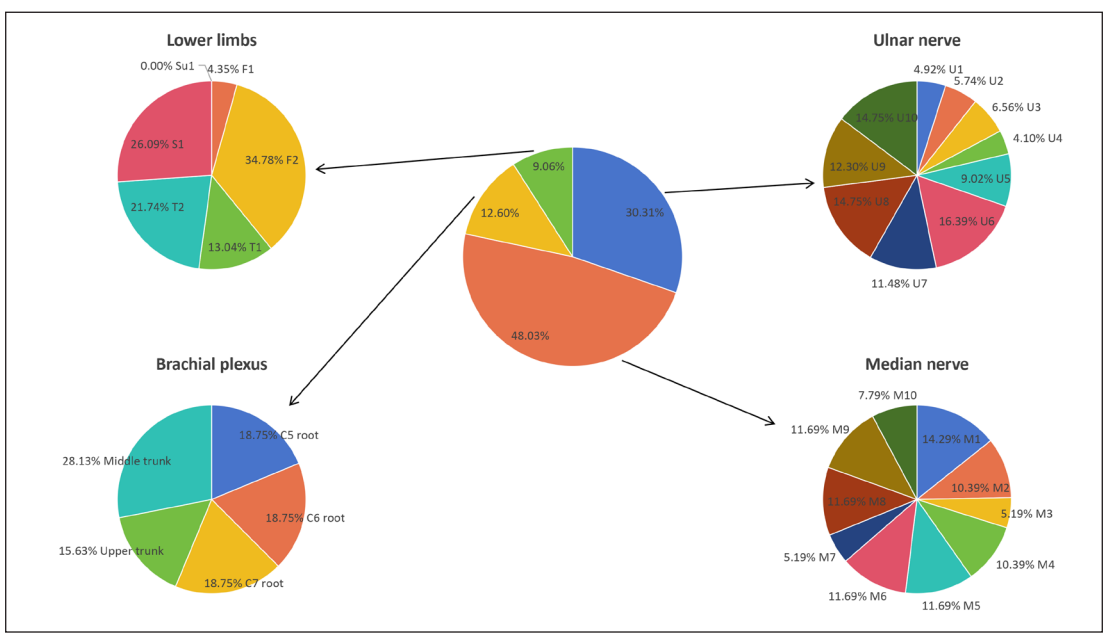

Figure 2. Distribution of nerve enlargement in vasculitic patients.

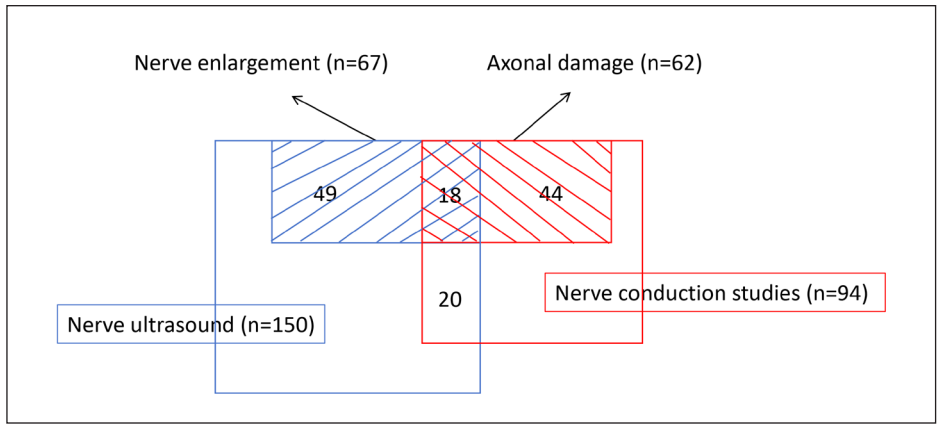

Figure 3. Relationship between nerve ultrasound and nerve conduction studies in vasculitic patients. Nerve conduction studies (NCS) and ultrasound were conducted on 150 and 94 nerves, respectively. Among them, 62 and 67 nerves reported nerve enlargement and axonal damage, respectivel. A total of 18 nerves reported abnormalities both in NCS and ultrasound, and other 20 nerves showed normal results both in NCS and nerve ultrasound.

polyneuropathy (CIDP) and Charcot-Marie-Tooth disease (CMT).[35,36] Moderate or marked nerve enlargement was detected in nearly half of the included patients, which was rare in patients with SLE, pSS or other axonopathy.[20] It was noteworthy that compared to HC, ssV patients tended to present decreased CSA in several sites of the median nerve and ulnar nerve (seen in our unpublished study). All these characteristics might play an essential role in the diagnosis and differential diagnosis of vasculitic neuropathy.

We noticed that the total disease duration of included ssV patients was significantly longer than that of psV patients and suspected the potential correlation between disease duration and nerve enlargement. However, no correlation was found between disease duration or laboratory findings and moderate or marked nerve enlargement, consistent with previous studies.[11,20] Further analysis suggested that marked nerve enlargement was more common in patients with newly reported limb weakness or numbness in the past

Table 3: Risk factors of moderate and marked nerve enlargement in primary systematic vasculitic patients

Factors	Over moderate nerve enlargement	Others	Comparisons
N	7	8	
Total disease duration (months)	50.14±71.90	19.00±16.79	0.254
Total treatment duration (months)	18.21±18.80	4.91±4.01	0.342
ESR (mm/h)	39.86±26.85	30.00±31.37	0.528
hsCRP (mg/L)	27.21±37.89	21.59±15.50	0.706
IgG (g/L)	9.07±3.00	9.75±4.40	0.737
IgA (g/L)	1.30±0.42	1.24±1.04	0.897
IgM (g/L)	2.31±1.00	2.40±1.00	0.857
C3 (g/L)	1.16±0.33	1.06±0.13	0.434
C4 (g/L)	0.26±0.13	0.23±0.06	0.456
ANCA (+)	42.86%	50.00%	0.782
BVAS	13.57±7.28	13.50±7.67	0.986
INCAT disability score	3.57±2.99	3.25±3.20	0.844

Abbreviations: ANCA anti-neutrophil cytoplasmic antibodies; BVAS the Birmingham Vasculitis Activity score; ESR erythrocyte sedimentation rate; hsCRP hypersensitive C-reactive protein; INCAT Inflammatory Neuropathy Cause and Treatment.

Note: Data were presented as mean±SD. Independent-sample t test or Chi test was used for comparisons and $P<0.05$ was considered as significance, which was bold.

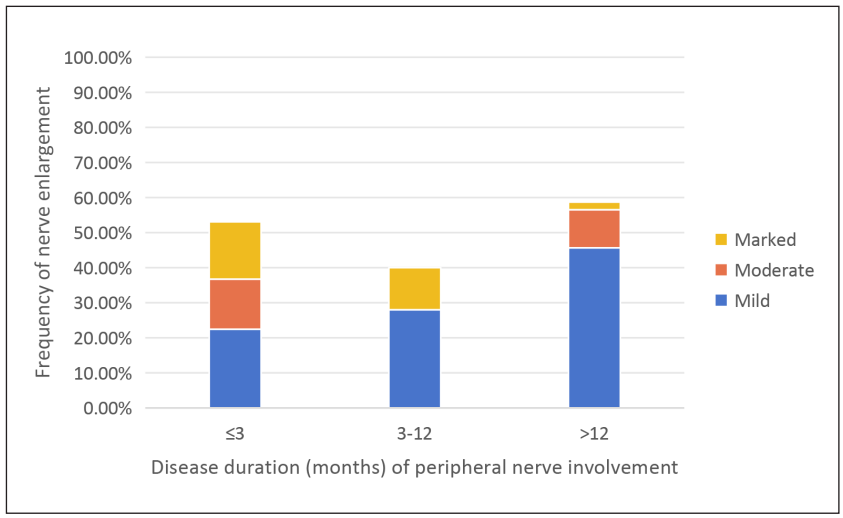

Figure 4. Frequency of nerve enlargement in vasculitic patients with different disease duration.

year. Kara *et al*. described a 48-year-old man with a very recent diagnosis of PAN and found remarkably enlarged and inhomogeneously anechoic fascicles of the patient's sciatic nerves.[37] Among our subjects, one PAN patient manifesting limb paralysis for 2 months showed multifocal and marked nerve enlargement, while the other presenting distal limb weakness and paresthesia showed only mild nerve enlargement under ultrasound. All these indicated that significant nerve enlargement might be the evidence of recent peripheral nerve involvement.

The detection rate of mild nerve enlargement increased with the disease duration of clinically peripheral nerve involvement. ANCA-related vasculitis and PAN were systemic vasculitides that commonly affected the epineural vessels in the vasa nervorum and produced peripheral neuropathies.[2] The vasculitic-granulomatous lesion in the epineurium, as well as intrafascicular edema as a consequence of nerve ischemia and axonal degeneration, might be responsible for the localized nerve enlargement based on pathological findings[38], which might be irreversible and accumulated over time. Therefore, we believed mild nerve enlargement might be a long-term condition or a sequela among patients with vasculitis. With further prolongation of disease duration, the gradual disappearance of edema and severe axonal degeneration might cause nerve atrophy, as seen in our ssV patients. Longitudinal ultrasonographic studies were needed to prove this.

The consistency between NCS and nerve ultrasound in detecting peripheral nerve involvement among vasculitic patients was not high, consistent with prior studies[11,20,39], especially in lower limbs. This might be due to the time required for structural and functional changes. In theory, changes in electrophysiology should precede changes in nerve ultrasound, and the formation of marked nerve thickening might take several months. The clinical manifestations of peripheral neuropathy might result from slowly cumulative damage in both function and structure.[40] Therefore, a combined examination using NCS and nerve ultrasound might be more effective in detecting vasculitic neuropathy.

Fascicle enlargement was detected in most included patients, which might reflect the predominantly axonal damage in vasculitic patients.[11] We did not conduct a subgroup analysis on fascicle enlargement to explore its clinical significance due to the limited number of included patients, which deserved future studies. Hypervascularization was common in our study population and might be related to an active inflammatory state of the peripheral nerve, as suggested by our analysis. However, we found no prominently increased level of inflammatory factors in patients with hypervascularization, possibly due to the influence of immunotherapy. Quantitative analysis of intraneural microvascular flow might better elucidate its significance.[41,42]

We admitted several limitations of the study. Firstly, the limited number of included patients disabled us for further analyses, especially regarding fascicle and marked nerve enlargement. Also, there might be vital differences in the distribution form of nerve enlargement among

different kinds of vasculitis, which were not discussed in the study. Secondly, there were significant differences in age and gender ratio between psV patients and controls, which might have a considerable effect on our results.[24,25] Thirdly, the cross-sectional study design did not allow us to explore the dynamic changes of CSA of peripheral nerves along with disease progression in vasculitic patients. Fourthly, at present, validated clinical outcome measures for vasculitis neuropathy are lacking, and the INCAT was not designed, nor has it been validated for use in vasculitis neuropathy. Also, the lack of relevant disease controls for vasculitis neuropathy might significantly limit the significance of our results. Lastly, immunotherapy might substantially influence our results, as all included patients underwent long-term steroid therapy. Multicenter and large-sample cohort studies were needed further to elucidate the clinical significance of HRUS in vasculitic neuropathy and facilitate the application of nerve ultrasound in vasculitis and other immune-mediated neuropathy.

In conclusion, nerve enlargement was common in patients with psV, mainly in multifocal distribution. Compared to patients with SLE or pSS, nerve enlargement in psV patients presented in more proximal segment with a higher degree. Marked nerve enlargement was significantly common in vasculitic patients with newly reported limb weakness or numbness in the past year. In contrast, the detection rate of mild nerve enlargement increased with the disease duration of clinically peripheral nerve involvement. A combined examination using NCS and nerve ultrasound might more effectively detect vasculitic neuropathy. Hypervascularization was common in psV patients and might be related to an active inflammatory state of the peripheral nerve.

DISCLOSURE

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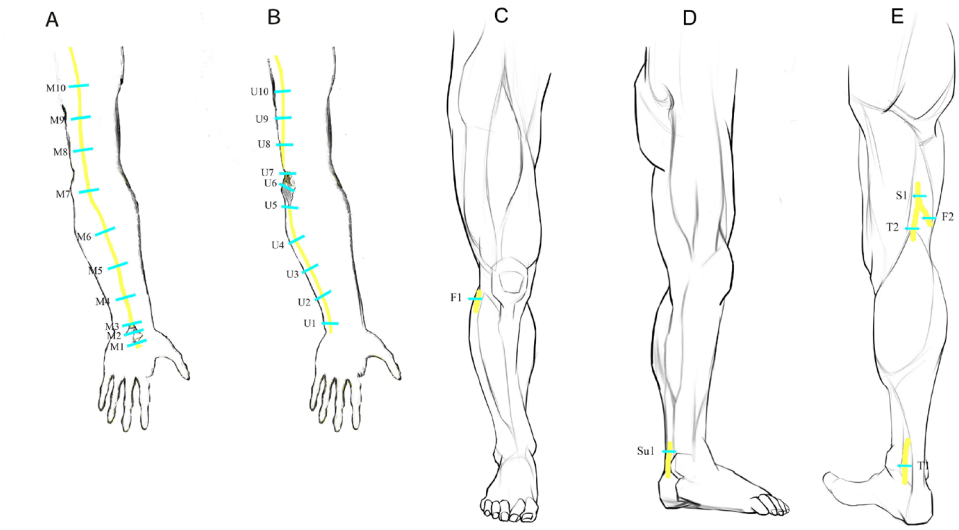
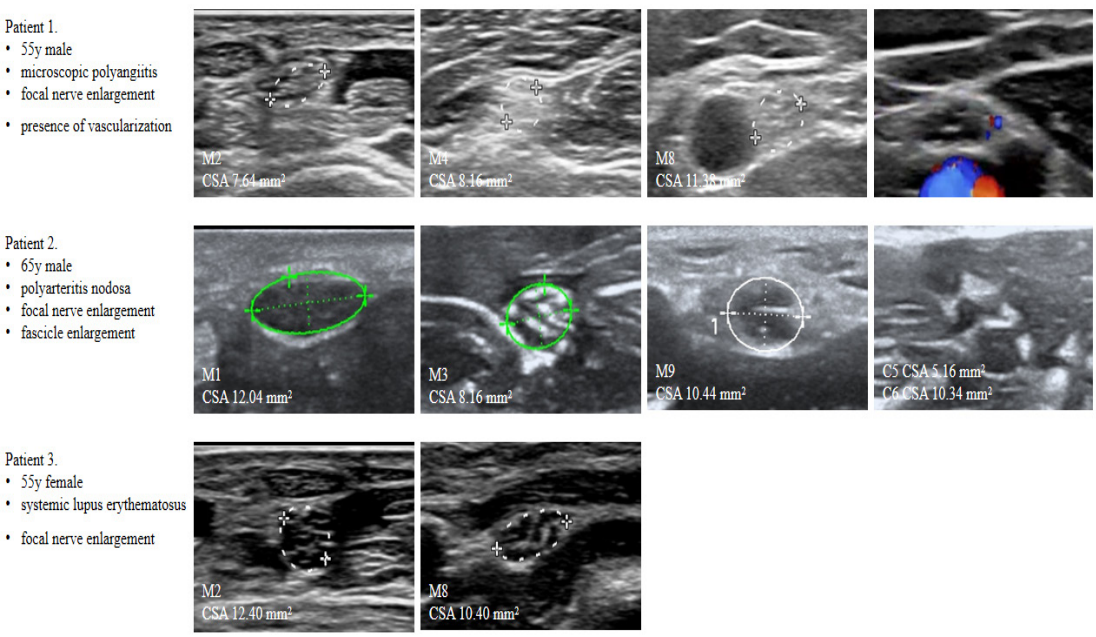
REFERENCES

1. Beachy N, Satkowiak K, Gwathmey KG. Vasculitic neuropathies. *Semin Neurol* 2019; 39(5):608-19. doi: 10.1055/s-0039-1688990.
2. Gwathmey KG, Burns TM, Collins MP, Dyck PJB. Vasculitic neuropathies. *Lancet Neurol* 2014; 13(1): 67-82. doi: 10.1016/S1474-4422(13)70236-9.
3. Collins MP, Dyck PJB, Gronseth GS, *et al*. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. *J Peripher Nerv Syst* 2010; 15(3): 176-84. doi: 10.1111/j.1529-8027.2010.00281.x.
4. Jennette JC, Falk RJ, Bacon PA, *et al*. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65(1): 1-11. doi: 10.1002/art.37715.
5. Wolf J, Schmitt V. Palm F, Grau AJ, Bergner R. Peripheral neuropathy as initial manifestation of primary systemic vasculitides. *J Neurol* 2013; 260(4): 1061-70. doi: 10.1007/s00415-012-6760-7.
6. Ando T, Watanabe H, Riku Y, *et al*. Neurogenic intermittent claudication caused by vasculitis in the cauda equina: an autopsy case report. *Eur Spine J* 2023; 32(7): 2602-6. doi: 10.1007/s00586-022-07458-7.
7. Alavi SAN, Meshkini M, Pourlak T, Khabbazi A. Microscopic polyangiitis complicated with bilateral brachial plexopathy: a case report and review of the literature. *Rheumatol Int* 2016; 36(7): 997-1001. doi: 10.1007/s00296-016-3424-4.
8. Collins MP, Arnold WD, J.T. Kissel JT. The neuropathies of vasculitis. *Neurol Clin* 2013; 31(2): 557-95. doi: 10.1016/j.ncl.2013.01.007.
9. Ito T, Kijima M, Watanabe T, Sakuta M, Nishiyama K. Ultrasonography of the tibial nerve in vasculitic neuropathy. *Muscle Nerve* 2007; 35(3): 379-82. doi: 10.1002/mus.20673.
10. Nodera H, Sato K, Terasawa Y, Takamatsu N, Kaji R. High-resolution sonography detects inflammatory changes in vasculitic neuropathy. *Muscle Nerve* 2006; 34(3): 380-1. doi: 10.1002/mus.20582.
11. Goedee HS, van der Pol WL, van Asseldonk JTH, *et al*. Nerve sonography to detect peripheral nerve involvement in vasculitis syndromes. *Neurol Clin Pract* 2016; 6(4): 293-303. doi: 10.1212/CPJ.0000000000000258.
12. Grimm A, Decard BF, Bischof A, Axer H. Ultrasound of the peripheral nerves in systemic vasculitic neuropathies. *J Neurol Sci* 2014; 347(1-2): 44-9. doi: 10.1016/j.jns.2014.09.017.
13. Grimm A, Decard BF, Axer H, Fuhr P. The Ultrasound pattern sum score - UPSS. A new method to differentiate acute and subacute neuropathies using ultrasound of the peripheral nerves. *Clin Neurophysiol* 2015; 126(11): 2216-25. doi: 10.1016/j.clinph.2015.01.011.
14. Üçeyler N, Schäfer KA, Mackenrodt D, Sommer C, Müllges W. High-resolution ultrasonography of the superficial peroneal motor and sural sensory nerves may be a non-invasive approach to the diagnosis of vasculitic neuropathy. *Front Neurol* 2016; 7: 48. doi: 10.3389/fneur.2016.00048.
15. Böhm J. [Assessment of peripheral nerves in vascular neuropathy with high-resolution ultrasonography] (in Hungarian). *Ideggyogy Sz* 2009. 62(7-8): 277-81.

16. Seeliger T, Bönig L, Gingele S, *et al*. Nerve ultrasound findings in Sjögren's syndrome-associated neuropathy. *J Neuroimaging* 2021. 31(6): 1156-65. doi: 10.1111/jon.12907.
17. Collins MP, Dyck PJB, Hadden RDM. Update on classification, epidemiology, clinical phenotype and imaging of the nonsystemic vasculitic neuropathies. *Curr Opin Neurol* 2019; 32(5): 684-95. doi: 10.1097/WCO.0000000000000727.
18. Zhang KJ, Li MX, Zhang P, Qin HQ, Guo ZN, Yang Y. Validity of high resolution magnetic resonance imaging in detecting giant cell arteritis: a meta-analysis. *Eur Radiol* 2022; 32(5): 3541-52. doi: 10.1007/s00330-021-08413-8.
19. Cartwright MS, Brown ME, Eulitt P, Walker FO, Lawson VH, Caress JB. Diagnostic nerve ultrasound in Charcot-Marie-Tooth disease type 1B. *Muscle Nerve* 2009; 40(1): 98-102. doi: 10.1002/mus.21292.
20. Grimm A, Heiling B, Schumacher U, Witte OW, Axer H. Ultrasound differentiation of axonal and demyelinating neuropathies. *Muscle Nerve* 2014; 50(6): 976-83. doi: 10.1002/mus.24238.
21. Niu J, Ding QY, Fan J, *et al*. Nerve ultrasound performances in differentiating POEMS syndrome from CIDP. *Neurotherapeutics* 2022; 19(2): 455-63. doi: 10.1007/s13311-022-01209-8.
22. Klauser AS, Buzzegoli T, Taljanovic MS, *et al*. Nerve entrapment syndromes at the wrist and elbow by sonography. *Semin Musculoskelet Radiol* 2018; 22(3): 344-53. doi: 10.1055/s-0038-1641577.
23. Yazici H, Tascilar K, Yazici Y. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria sets for three types of antineutrophilic cytoplasmic antibody-associated vasculitis. *Curr Opin Rheumatol* 2023; 35(1): 1-5. doi: 10.1097/BOR.0000000000000916.
24. Niu J, Li Y, Zhang L, Ding QY, Cui LY, Liu MS. Cross-sectional area reference values for sonography of nerves in the upper extremities. *Muscle Nerve* 2020; 61(3): 338-46. doi: 10.1002/mus.26781.
25. Niu J, Li Y, Zhang L, Ding QY, Cui LY, Liu MS. Reference values for lower limb nerve ultrasound and its diagnostic sensitivity. *J Clin Neurosci* 2021; 86: 276-83. doi: 10.1016/j.jocn.2021.01.013.
26. Kimura J. Assessment of individual nerves. Techniques to assess muscle function. In: Kimura J, ed. Electrodiagnosis in diseases of nerve and muscle: principles and practice, 3rd ed. New York: Oxford University Press; 2001: 130-171, 307-32.
27. Mukhtyar C, Lee R, Brown D, *et al*. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68(12): 1827-32. doi: 10.1136/ard.2008.101279.
28. Breiner A, Barnett C, Bril V. INCAT disability score: a critical analysis of its measurement properties. *Muscle Nerve* 2014; 50(2): 164-9. doi: 10.1002/mus.24207.
29. Grimm A, Winter N, Rattay TW, *et al*. A look inside the nerve - Morphology of nerve fascicles in healthy controls and patients with polyneuropathy. *Clin Neurophysiol* 2017; 128(12): 2521-6. doi: 10.1016/j.clinph.2017.08.022.
30. Paluch Ł, Noszczyk BH, Walecki J, Osiak K, Kiciński M, Pietruski P. Shear-wave elastography in the diagnosis of ulnar tunnel syndrome. *J Plast Reconstr Aesthet Surg* 2018; 71(11): 1593-9. doi: 10.1016/j.bjps.2018.08.018.
31. Bouche P, Léger JM, Travers MA, Cathala HP, Castaigne P. Peripheral neuropathy in systemic vasculitis: clinical and electrophysiologic study of 22 patients. *Neurology* 1986; 36(12): 1598-602. doi: 10.1212/wnl.36.12.1598.
32. Collins MP, Periquet MI, Mendell JR, Sahenk Z, Nagaraja HN, Kissel JT. Nonsystemic vasculitic neuropathy: insights from a clinical cohort. *Neurology* 2003; 61(5): 623-30. doi: 10.1212/01.wnl.0000082715.48844.3e.
33. Seo JH, Ryan HF, Claussen GC, Thomas TD, Oh SJ. Sensory neuropathy in vasculitis: a clinical, pathologic, and electrophysiologic study. *Neurology* 2004; 63(5): 874-8. doi: 10.1212/01.wnl.0000137017.45065.3e.
34. Hildebrand A, Scheiber F, Weber L, *et al*. Peripheral nerve ultrasound for the differentiation between ALS, inflammatory, and hereditary polyneuropathies. *Medicina* (Kaunas) 2023; 59(7):1192. doi: 10.3390/medicina59071192.
35. Fionda L, Di Pasquale A, Morino S, *et al*., Changes of clinical, neurophysiological and nerve ultrasound characteristics in CIDP over time: a 3-year follow-up. *J Neurol* 2021; 268(8): 3011-9. doi: 10.1007/s00415-021-10485-x.
36. Zanette G, Fabrizi GM, Taioli F, *et al*. Nerve ultrasound findings differentiate Charcot-Marie-Tooth disease (CMT) 1A from other demyelinating CMTs. *Clin Neurophysiol* 2018; 129(11): 2259-67. doi: 10.1016/j.clinph.2018.08.016.
37. Kara M, Ozçakar L. Ultrasonographic imaging of the sciatic nerves in a patient with polyarteritis nodosa. *Rheumatol Int* 2012; 32(10): 3327-8. doi: 10.1007/s00296-011-2138-x.
38. Mitsumoto H, Levin KH, Wilbourn AJ, Chou SM. Hypertrophic mononeuritis clinically presenting with painful legs and moving toes. *Muscle Nerve* 1990; 13(3): 215-21. doi: 10.1002/mus.880130308.
39. Beekman R, van den Berg LH, Franssen H, Visser LH, van Asseldonk JTH, Wokke JHJ. Ultrasonography shows extensive nerve enlargements in multifocal motor neuropathy. *Neurology* 2005; 65(2): 305-7. doi: 10.1212/01.wnl.0000169179.67764.30.
40. Bortoluzzi A, Silvagni E, Furini F, Piga M, Govoni M. Peripheral nervous system involvement in systemic lupus erythematosus: a review of the evidence. *Clin Exp Rheumatol* 2019; 37(1): 146-55.
41. Goedee HS, Brekelmans GJ, Visser LH. Multifocal enlargement and increased vascularization of peripheral nerves detected by sonography in CIDP: a pilot study. *Clin Neurophysiol* 2014; 125(1): 154-9. doi: 10.1016/j.clinph.2013.05.025.
42. Frijlink DW, Brekelmans GJ, Visser LH, Increased nerve vascularization detected by color Doppler sonography in patients with ulnar neuropathy at the elbow indicates axonal damage. *Muscle Nerve* 2013; 47(2): 188-93. doi: 10.1002/mus.23505.



Supplementary Figure 1. Predetermined sites of peripheral nerves for detection.
A. The ten sites of median nerve: the outlet of carpal tunnel (M1), the middle point of wrist crease (M2), the inlet of carpal tunnel (M3), 4 cm proximal to wrist crease (M4), middle between wrist crease and elbow (M5), entrance before into pronator teres (M6), elbow (M7), 4 cm above elbow (M8), 8 cm above elbow (M9), axilla (M10).
B. The ten sites of ulnar nerve: wrist (U1), 4 cm proximal to wrist (U2), departing point from ulnar artery (U3), alongside the muscle belly of flexor carpi ulnaris (U4), outlet of cubital tunnel (U5), inside cubital tunnel (U6), inlet of cubital tunnel (U7), 4 cm proximal to inlet of cubital tunnel (U8), 8 cm proximal to inlet of cubital tunnel (U9), axilla (U10).
C. The one site of sural nerve: the distal calf, approximately 5 cm proximal to the ankle (Su1).
DE. The two sites of tibial nerve: the ankle (T1), the popliteal fossa (T2). The two sites of fibular nerve: the fibular head (F1) and the popliteal fossa (F2). The one site of sciatic nerve: the distal part of thigh, just proximal to the convergence of tibial and fibular nerve (S1).



Supplementary Figure 2. Examples of ultrasonic abnormalities in vasculitic patients.

Supplementary Table 1: Risk factors of increased intraneural vascular flow in primary systemic vasculitic patients

Factors	Increased intraneural vascular flow	Others	Comparisons
N	8	7	
Total disease duration (months)	24.34±29.30	44.00±69.72	0.479
Total treatment duration (months)	6.63±6.81	16.25±15.51	0.552
ESR (mm/h)	28.38±25.47	41.71±32.59	0.390
hsCRP (mg/L)	26.03±31.02	22.13±24.56	0.794
IgG (g/L)	7.44±2.38	11.71±3.73	**0.019**
IgA (g/L)	0.90±0.48	1.69±0.89	**0.048**
IgM (g/L)	2.07±0.97	2.70±0.91	0.218
C3 (g/L)	1.10±0.25	1.12±0.25	0.878
C4 (g/L)	0.27±0.10	0.20±0.09	0.343
ANCA (+)	71.43%	37.50%	0.189
BVAS	15.50±7.13	11.29±7.16	0.275
INCAT disability score	3.88±2.64	2.86±3.49	0.532

Abbreviations: ANCA anti-neutrophil cytoplasmic antibodies; BVAS the Birmingham Vasculitis Activity score; ESR erythrocyte sedimentation rate; hsCRP hypersensitive C-reactive Vasculitis Activity score; ESR erythrocyte sedimentation rate; hsCRP hypersensitive C-reactive protein; INCAT Inflammatory Neuropathy Cause and Treatment. protein; INCAT Inflammatory Neuropathy Cause and Treatment.

Note: Data were presented as mean±SD. Independent-sample t test or Chi test was used for Note: Data were presented as mean±SD. Independent-sample t test or Chi test was used for comparisons and $P<0.05$ was considered as significance, which was bold. comparisons and $P<0.05$ was considered as significance, which was bold.