Clinical characteristics, brain magnetic resonance imaging findings and diagnostic approach of the primary central nervous system vasculitis according to angiographic classification

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Abstract

Objective

To determine the diagnostic accuracy for high-resolution vessel wall image (HR-VWI) and brain biopsy according to angiographical classification in patients with primary central nervous system vasculitis (PCNSV).

Methods

We extracted the patients with PCNSV who underwent the complete brain MRI protocol and cerebral vascular image from Cleveland Clinic prospective CNS vasculopathy Bioregistry. The large-medium vessel variant (LMVV) was defined as patients with cerebral vasculature indicating vasculitis in proximal or middle arterial segments, whereas vessel involvements in smaller distal branches or normal angiography were considered as the small vessel variant (SVV). We compared clinical demographics, magnetic resonance imaging (MRI) findings, and diagnostic approaches between two variants.

Results

In this case-control study that included 34 PCNSV patients, the LMVV group comprised a total of 11 patients (32.4%), and 23 patients (67.6%) were classified as the SVV group. The LMVV had more strong/concentric vessel wall enhancement on HR-VWI (LMVV: 90% (9/10) vs. SVV: 7.1% (1/14), p<0.001). By contrast, meningeal/parenchymal contrast enhancement lesion was more frequently observed in the SVV group (p=0.006). The majority of SVV was diagnosed by brain biopsy (SVV: 78.3% vs. LMVV: 30.8%, p=0.022). The diagnostic accuracy of the brain biopsy was 100% (18/18) in SVV and 57.1% (4/7) in LMVV, respectively (p=0.015).

Conclusion

Diagnostic approach for PCNSV differs concerning the affected vessel size. HR-VWI is a useful imaging modality for the diagnosis of LMVV. Brain biopsy remains the gold standard for proving PCNSV with SVV but is still positive in almost one-third of LMVV.

Key words

central nervous system vasculitis, magnetic resonance imaging, brain biopsy, angiography, diagnostic approach

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Introduction

Primary central nervous system vasculitis (PCNSV) is a rare and poorly understood inflammatory disorder limited to the CNS vessels (1, 2). Diagnostic criteria for PCNSV were proposed by Calabrese and Mallek based on clinical experience and literature reviews (3). These criteria have been used widely for clinical practice and investigation. In 2009, Binbaum and Hellmann proposed a classification based on the certainty of the diagnosis; definite for biopsy-proven PCNSV, and probable for image-based PCNSV without histological confirmation but with a high-probability angiogram, an abnormal magnetic resonance imaging (MRI), and inflammatory cerebrospinal fluid (CSF) profiles (4). Diagnosis of PCNSV remains challenging due to the presence of wide mimicking conditions such as reversible cerebral vasoconstriction syndrome (RCVS) (5-8), intracranial atherosclerosis (9, 10), CNS lymphoma (11, 12), infection [*e.g.* varicella-zoster virus (13), aspergillosis (14), and tuberculosis (15)], which have similar clinical presentations, MRI patterns, and cerebral angiogram findings.

PCNSV patients represent a wide range of MRI spectrums including brain infarcts, extensive white matter lesion, parenchymal haemorrhage, subarachnoid haemorrhage, tumour-like lesion, and leptomeningeal/parenchymal enhancement lesion (8, 16-18). The sensitivity of MRI in these patients is close to 100% in the literature (8, 16-18). Recently, high-resolution MRI vessel wall imaging (HR-VWI) has been investigated to characterise vessel wall patterns of PCNSV and other non-inflammatory intracranial vasculopathy (19-21). Concentric arterial wall thickening with strong vessel wall enhancement (VWE) has been considered a consistent pattern in PCNSV (19-23), which is presumably secondary to increased permeability of the endothelium and vasa vasorum-related contrast leakage from the lumen into the arterial wall (22). HR-VWI has the potential to be used to differentiate mimics (19-22), assess vasculitis activity (23, 24), and select the targeting biopsy site (25). With the emergence of HR-VWI, many rely on this technique for the diagnosis of PCNSV, especially within the large vessel category. However, visualisation of the wall characteristic of the small sized-intracranial vessels is beyond the spatial resolution and the current HR-VWI technique has a limited capacity for evaluation of the smaller distal involvements (22). Despite the advance in non-invasive neuroimaging modalities, digital subtraction angiography (DSA) remains the gold standard to detect smooth segmental narrowing or dilation in the cerebral arteries (26, 27). The evaluation of intracranial smaller distal branch vessels requires this invasive procedure for the diagnosis of PCNSV without histological validation (28, 29).

In addition to the current diagnostic classification, two different subtypes of the disease have emerged in the literature, the small vessel variant (SVV) and large/medium vessel variant (LMVV) by affected vessel size (30-32). The SVV was ascertained primarily through histological confirmation (30-32). However, only 50 to 60% of image-based PCNSV patients showed abnormal CSF findings in these cohorts (30-32). Therefore, the difference in eligibility criteria for image-based PCNSV raises the possibility that some patients might include other mimicking intracranial vasculopathy in previous reports (30-32). We hypothesised that the image profiles and diagnostic approaches would vary between LMVV and SVV in patients with PCNSV. This study aimed to clarify the clinical characteristics, brain MRI findings, and diagnostic accuracy for HR-VWI and brain biopsy according to affected vessel size in PCNSV patients from our prospective CNS vasculopathy registry.

Subjects and methods

Study design and cohort

We included all patients with PCNSV from the prospective CNS vasculopathy Bioregistry. This bioregistry was initiated in 2012 till the present and includes patients with PCNSV as well as other vasculopathy that mimic PCNSV such as RCVS, moyamoya disease, arterial dissection, intracranial atherosclerosis, secondary cause of vasculi-

tis, amyloid angiopathy, and unknown cause of intra-cranial vasculopathy. Extensive clinical, laboratory, imaging modalities, biological specimens, and outcome measures are obtained on all patients upon diagnosis and follow-up. This bioregistry has been approved by Cleveland Clinic Institutional Review Board; written informed consent was obtained from all patients or relatives before the study.

Clinical characteristics

A total of 512 variables were collected for all patients at the registration. These include: 1) demographics; 2) the date of symptom onset; 3) vascular risk factors; 4) the previous history of stroke; 5) clinical symptoms including headache, seizure, weakness, cognitive impairments, and visual symptoms. Further, multiple outcome measures were collected including modified Rankin scale (mRS) score (33), Barthel Index (34), Brief Patient Health Questionnaire (BPHQ-9) (35), and European Quality of Life Questionnaire (EQOL) (36).

Diagnosis of PCNSV

Patients were included in the study if they met clinical diagnostic criteria proposed by Calabrese and Mallek (3); namely: 1) the presence of an unexplained neurologic deficit after thorough clinical and laboratory evaluation; 2) documentation by cerebral angiography and/or tissue examination of an arteritic process within the central nervous system; and 3) no evidence of a systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary. Biopsy-proven PCNSV was considered to be the presence of granulomatous, lymphocytic, or necrotising vasculitis of medium to small size vessels in the brain tissue specimens (37-39). In cases without evidence of histological confirmation, the diagnosis of PCNSV was made according to the clinical pictures, MRI abnormalities, cerebral vascular imaging, and inflammatory CSF profiles (4). All neuroimages were evaluated by an experienced neurologist (T.S., 12 years of experience), blinded to clinical, laboratory, and pathological findings. Images were discussed with an expert neurologist (KU) and rheumatologist (R.H.A) when confirming the diagnosis of PCNSV. The neuroimage findings with consensus judgment were used for analysis. Image-based PCNSV was defined as if patients met all four of the following findings; 1) multifocal segmental narrowing, dilations, and/or occlusion on the DSA (26-29), 2) brain MRI abnormalities, 3) inflammatory CSF profiles, and 4) no evidence of systemic vasculitis (40) or any other mimicking conditions (5-15). Finally, the diagnosis of all PCNSV cases was made by expert rheumatologist (R.H.A) and neurologist (K.U).

All patients were followed over a median time of 16.0 months to ensure the accuracy of the final diagnosis. Relapse was defined as a new neurological event associated with new significant radiological abnormalities (new cerebral infarct, the extension of white matter lesion, appearance of gadolinium enhancements, and worsening of arterial stenosis), leading to an intensification of treatment by the treating physician (37).

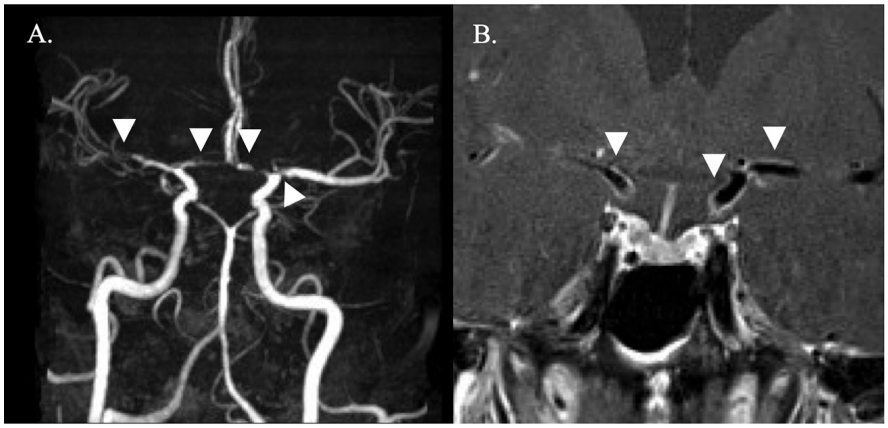

Fig. 1. Example of quantitative VWE score (Case 10: A 53-year-old woman with LVV).
A: TOF-MRA revealing multiple intracranial stenoses at the right M1 distal to M2 portion, bilateral A1 segments, and left M1 proximal segment (arrowheads).
B: Coronal HR-VWI demonstrating strong/concentric VWE on the right ICA (2 points), left ICA (2 points), and left M1 (2 points). A total of eight arterial segments with strong/concentric VWE were observed in HR-VWI. The total VWE score was 16.

Brain MRI findings

Brain MRI was performed using a commercially available echo-planar instrument operating at 3.0 Teslas (Skyra or Trio; Siemens, Erlangen, Germany). Diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), T1-weighted imaging, T2-weighted imaging, T2*weighted imaging, or susceptibility-weighted imaging (SWI), and gadolinium-enhanced T1-weighted imaging were performed routinely in PCNSV patients. Lesions on brain MRI were classified as brain infarcts, parenchymal haemorrhage, subarachnoid haemorrhage, white matter lesion, tumour-like lesion, and contrast enhancement lesion in leptomeninges or cerebral parenchyma (8, 16-18).

HR-VWI and cerebral vascular imaging

HR-VWI protocol included 2D black-blood contrast-enhanced T1-weighted sequences and time-of-flight MRA of the circle of Willis. Detailed protocol, sequence, and acquisition of MRA and HR-VWI at Cleveland Clinic have been reported previously (21). The following intracranial vessel segments were assessed on HR-VWI: internal carotid artery (ICA: C4-C7 segment), anterior cerebral artery (ACA: A1, A2 segment), middle cerebral artery (MCA: M1, M2 segment), posterior cerebral artery (PCA: P1, P2 segment), vertebral artery (VA: V4 segment), and basilar artery (BA: union-top). The presence or absence of VWE was determined by comparing pre-gadolinium and post-gadolinium vessel wall imaging. VWE grade was classified on a 3-point scale: 0, none or signal equal to that of the pre-contrast image; 1, eccentric enhancement if there was clearly non-uniform

Table I. Baseline characteristics among all, LMVV and SVV in patients with PCNSV.

	All (n=37)	LMVV (n=11)	SVV (n=23)	*p*-value
Age, median (IQR); years	48 (36-57)	47 (35-53)	49 (36-58)	0.445
Interval from onset to registration, median (IQR); years	1.3 (0.4-3.6)	2.1 (0.2-3.7)	1.2 (0.4-3.1)	0.561
Male, n (%)	22 (59.5)	5 (45.5)	16 (69.6)	0.262
Stroke risk factors, n (%)				
Hypertension	14 (37.8)	5 (45.5)	8 (34.8)	0.709
Hyperlipidaemia	9 (24.3)	2 (18.2)	7 (30.4)	0.682
Diabetes	8 (21.6)	5 (38.5)	4 (17.4)	0.388
Smoking	8 (21.6)	2 (18.2)	6 (26.1)	1.000
Stroke	21 (56.8)	9 (81.8)	12 (52.2)	0.140
Clinical symptoms, n (%)				
Headache	26 (70.3)	6 (54.5)	18 (78.3)	0.232
Seizure	10 (27.0)	1 (9.1)	8 (34.8)	0.214
Weakness	21 (56.8)	9 (81.8)	11 (47.8)	0.076
Cognitive impairment	10 (27.0)	2 (18.2)	8 (34.8)	0.437
Visual symptoms	12 (32.4)	5 (45.5)	7 (30.4)	0.459
Modified Rankin Scale, median (IQR)	2 (1-3)	2 (1-4)	2 (1-3)	0.772
Relapse, n (%)	12 (32.4)	7 (58.3)	5 (21.7)	0.059
Barthel Index, median (IQR)	95 (44-100)	73 (16-100)	95 (45-100)	0.428
PHQ-9 score, median (IQR)	9 (5-12)	12 (4-15)	10 (5-13)	0.776
Euro-QOL subscales, median (IQR)				
Mobility	1 (1-2)	1.5 (1-3)	2 (1-3)	0.728
Self-care	1 (1-2)	1.5 (1-3)	1 (1-2)	0.392
Usual activities	2 (1-3)	2 (1-3)	2 (1-2.5)	0.636
Pain discomfort	2 (1-2)	2 (1.5-2)	1 (1-2)	0.190
Anxiety/depression	2 (1-2)	2 (1-2.5)	2 (1-2)	0.875

LMVV: large/medium vessel variant; SVV: small vessel variant; PCNSV: primary central nervous system vasculitis; PHQ-9: patient health questionnaire-9; Euro-QOL: European quality of life questionnaire.

and non-circumferential thin-wall artery with mild hyperintensity; 2, concentric enhancement if there was the whole wall circumference and thick-wall artery with strong hyperintensity (23). We assessed the quantitative VWE score (Fig. 1) based on the number of arterial segments with VWE (23).

We principally demonstrated TOF-MRA to assess the arterial involvement, because MRA can also be available concomitantly with HR-VWI and comparable to each finding for concordance of abnormalities. In all patients without clear evidence of histological confirmation, we conducted DSA to evaluate the cerebral vasculature in detail. DSA included injection of both common/internal carotid arteries and the dominant vertebral artery through the late venous phase. Angiographic imaging was performed at each selected vessel. LMVV was defined as patients with angiographic changes indicating vasculitis in proximal (ICA, M1, A1, P1, VA, BA) or middle (M2, A2, P2) arterial segments (27). The current HR-VWI technique has a limited capacity for evaluation of the smaller distal branches beyond the spatial resolution (22). In this study, we modified the angiographic criteria proposed by Thaler *et al*. (28). SVV was diagnosed with multifocal segmental narrowing/occlusion and dilations in only smaller distal branches (8) or without evidence of vessel involvement on the MRA or DSA (28).

CSF analysis

CSF analysis is a crucial assessment for patients with PCNSV and approximately 80% of PCNSV patients revealed abnormal CSF findings in biopsy-proven cases (1, 2). Abnormal CSF was defined by either leukocyte counts >5 cells/mm3 (pleocytosis) or protein level >45 mg/dl (elevated protein) (38). In the present study, abnormal CSF finding is mandatory for the diagnosis of image-based PCNSV (38).

Statistical analysis

First, all patients were classified into the LMVV group and the SVV group according to the affected vessel size on MRA or DSA. Clinical characteristics, neuroimaging, CSF, and brain biopsy findings were compared across these two groups. Next, patients were divided into four subgroups according to affected vessel size (LMVV or SVV) and diagnostic process (biopsy-proven or image-based). Neuroimaging and CSF findings were then compared between the four subgroups. Finally, we presented detailed neuroimaging, CSF, and brain biopsy findings in all LMVV and SVV patients. Continuous variables are expressed as the median and interquartile range (IQR) in the text and tables due to non-normal distribution. The significance of intergroup differences was assessed using a χ^2 test for categorical variables and a Mann-Whitney U-test for continuous variables in univariate analysis. Values of $p<0.05$ were considered to indicate statistically significant differences. All statistical analyses were performed using Statistical Package for the Social Sciences software for Windows (SPSS v. 25.0, Chicago, IL).

Results

A total of 201 patients were enrolled in the Cleveland Clinic prospective CNS vasculopathy registry from March 2012

to December 2019. Among them, 37 PCNSV patients met the inclusion criteria (22 males; median age 48 [36-57]) years; the median interval from onset to registration was 1.3 [0.4-3.6] years) (Table I). Of these, we excluded three biopsy-proven PCNSV patients due to no investigation of the complete brain MRI protocol and cerebral vascular image. The remaining 34 patients (both DSA and MRA: n=24, only MRA: n=8, only DSA: n=2) were analysed in the present study (Fig. 2).

Baseline clinical characteristics

Table I shows the baseline clinical characteristics of all cohorts, the LMVV, and the SVV groups. The LMVV group comprised a total of 11 patients (32.4%), and 23 patients (67.6%) were classified as the SVV group. Age, sex, the interval from onset to enrolment, stroke risk factors, and previous stroke history were similar between the LMVV, and the SVV groups. Clinical symptoms and outcomes did not show significant differences between the LMVV, and the SVV groups. Relapse was observed in 12 of 37 (32.4%) PCNSV patients during the follow-up (median time: 16.0 months). The prevalence rate of relapse was relatively higher in the LMVV group than in the SVV group, but not statistically significant (LMVV: 58.3% *vs*. SVV: 21.7%, p=0.059).

Brain MRI, cerebral vascular image, and HR-VWI findings

Table II summarises the brain MRI, cerebral vascular image, and HR-VWI findings. Regarding the cerebral vascular image modalities, all LMVV patients underwent both DSA and MRA. By contrast, 8 of 23 (34.8%) SVV patients assessed the cerebral vasculature by only MRA, because the diagnosis of PCNSV was confirmed pathologically in all of these cases (Table VI). In brain MRI findings, brain infarcts were more common in the LMVV group than in the SVV group (LMVV: 100.0 % *vs*. SVV: 60.9%, p=0.017). Tumour-like lesion (SVV: 34.8% *vs*. LMVV: 0.0%, p=0.034; Fig. 3) and contrast enhancement lesion (SVV: 87.0% *vs*. LMVV: 45.5%, p=0.033; Fig. 4) were more frequently observed in the SVV group than in the LMVV group. By definition, all LMVV patients had significant vessel involvements in the proximal or middle arterial segment on the DSA. Moreover, 10 of 11 (90.9 %) LMVV patients also had small distal branch involvements in the DSA (Table V). HR-VWI was performed on a total of 24 patients (LMVV: 10 of 11 patients; SVV: 13 of 23 patients). VWE was identified in all LMVV patients (LMVV: 100.0% (10/10) vs. SVV: 14.4% (2/14), p<0.001). The prevalence of strong/concentric VWE was significantly

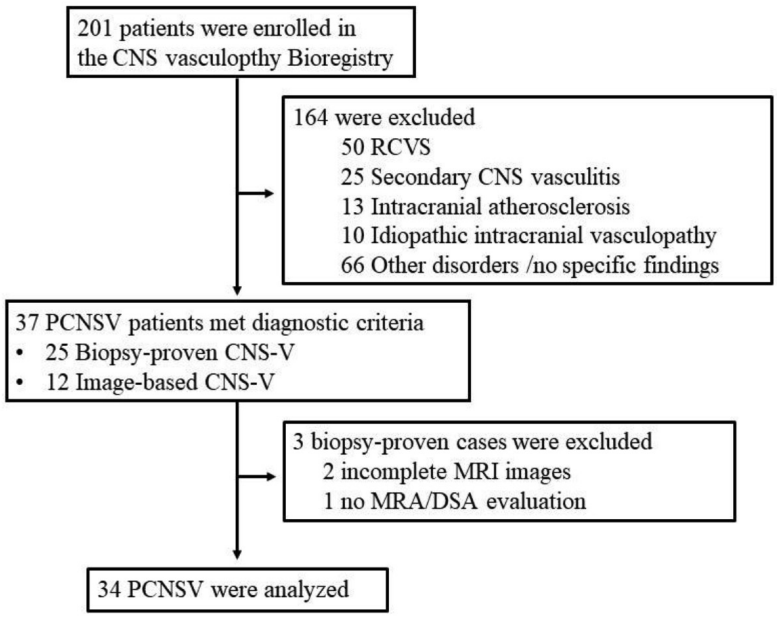

Fig 2. Study flow diagram.

Table II. Brain MRI, cerebral angiogram, and HR-VWI findings between LMVV and SVV in PCNSV patients.

	LMVV (n=11)	SVV (n=23)	p value
MRI findings, n (%)			
Brain infarcts	11 (100.0)	14 (60.9)	0.017
Parenchymal haemorrhage	1 (9.1)	5 (21.7)	0.638
Subarachnoid haemorrhage	0 (0.0)	4 (17.4)	0.280
White matter lesion	2 (18.2)	12 (52.2)	0.076
Tumour-like lesion	0 (0.0)	8 (34.8)	0.034
Contrast enhancement lesion	5 (45.5)	20 (87.0)	0.033
Assessment of the cerebral vascular image, n (%)			
Both MRA and DSA	11 (100.0)	13 (56.5)	0.014
Only MRA	0 (0.0)	8 (34.8)	0.034
Only DSA	0 (0.0)	2 (8.7)	1.000
Arterial stenosis, n (%)			
Proximal segment	7 (63.6)	0 (0.0)	<0.001
Middle segment	10 (90.9)	0 (0.0)	<0.001
Smaller distal branch	10 (90.9)	8 (34.8)	0.003
None	0 (0.0)	15 (65.2)	<0.001
HR-VWI findings, n (%)			
VWE	10 (100.0)[n=10]	2 (14.3) [n=14]	<0.001
Strong/concentric VWE	9 (90.0) [n=10]	1 (7.1) [n=14]	<0.001
Mild/eccentric VWE	1 (10.0) [n=10]	1 (7.1) [n=14]	1.000
VWE score	3 (2-17) [n=10]	0 (0-0) [n=14]	<0.001

MRI: magnetic resonance imaging; HR-VWI: high-resolution vessel wall image; LMVV: large/medium vessel variant; SVV: small vessel variant; PCNSV: primary central nervous system vasculitis; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; VWE: vessel wall enhancement; CSF: cerebral spinal fluid.
*Abnormal CSF is defined by either leukocyte counts >5 cells/mm^3 (pleocytosis) or protein level >45 mg/dl (elevated protein).

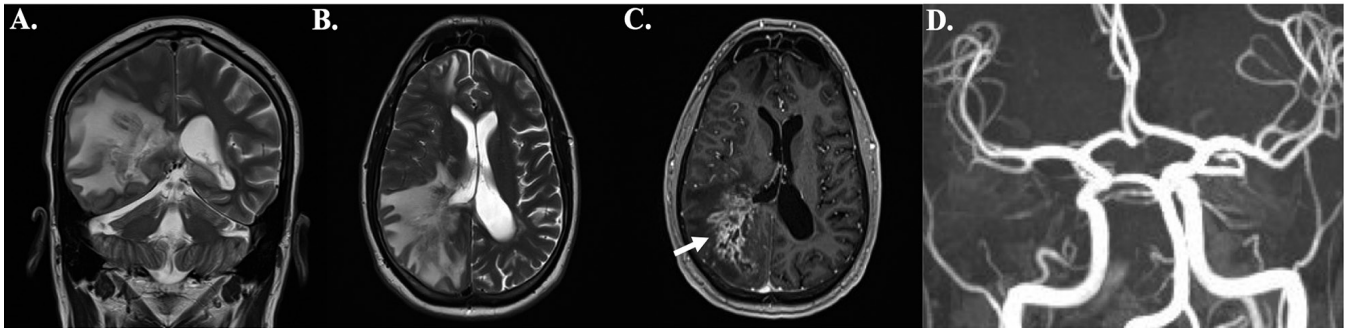

Fig. 3. A brain MRI showed a tumour-like lesion in the SVV (Case 33: biopsy-proven).
A-**B**: Coronal and axial T2 weighted images showing massive lesion with surrounding oedema in the right parieto-temporal lobe highly suggestive of glioma.
C: Axial gadolinium-enhanced MRI demonstrating irregular enhancement lesion inside of the tumour-like presentation(arrow).
D: MRA revealing no significant vessel involvements.

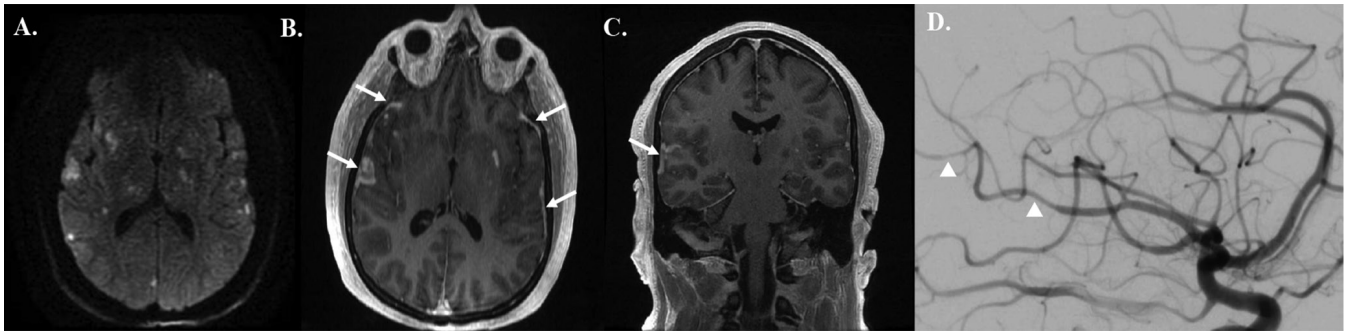

Fig. 4. A brain MRI showed multiple infarcts and leptomeningeal/parenchymal enhancement lesions in the SVV (Case 17: biopsy-proven).
A: Axial DWI showing disseminated small acute infarcts in the bilateral hemisphere.
B-**C**: Axial and coronal gadolinium-enhanced MRI demonstrating enhancement lesion in the leptomeninges and cortex (arrows).
D: DSA revealing segmental smooth vessel irregularities in the distal MCA branch (arrowheads).

higher in the LMVV group than in the SVV group (LMVV: 90.0% (9/10) *vs*. SVV: 7.2% (1/14), $p<0.001$). Similarly, the VWE score was significantly higher in the LMVV group than in the SVV group (LMVV: 3 *vs*. SVV: 0, $p<0.001$).

Brain biopsy and CSF findings

Table III summarises the brain biopsy and CSF findings. The majority of SVV was proven by brain biopsy (SVV: 78.3% *vs*. LMVV: 36.4%, $p=0.026$). The positive rate of the brain biopsy was 100% (18/18) in SVV and 57.1% (4/7) in LMVV, respectively ($p=0.015$). There were no significant differences in the histological patterns between the two groups ($p=0.490$ for granulomatous vasculitis, $p=0.378$ for lymphocytic vasculitis, and $p=0.274$ for necrotising vasculitis). No significant differences were observed in the CSF findings between the two groups ($p=0.269$ for abnormal CSF findings, $p=0.106$ for pleocytosis, and $p=1.000$ for elevated protein).

Table III. Brain biopsy and CSF findings between LMVV and SVV in PCNSV patients.

	LMVV (n=11)	SVV (n=23)	*p* value
Biopsy-proven PCNSV, n (%)	4 (36.4)	18 (78.3)	0.026
Biopsy positive, n (%)	4 (57.1) [n=7]	18 (100.0) [n=18]	0.015
Pathological patterns, n (%)			
Granulomatous vasculitis	1 (14.3) [n=7]	1 (11.1) [n=18]	0.490
Lymphocytic vasculitis	3 (42.9) [n=7]	12 (66.7) [n=18]	0.378
Necrotising vasculitis	0 (0.0) [n=7]	5 (27.8) [n=18]	0.274
CSF findings, n (%)			
Abnormal *	11 (100.0) [n=11]	16 (80.0) [n=20]	0.269
Pleocytosis *	10 (90.9) [n=11]	12 (60.0) [n=20]	0.106
Elevated protein*	8 (72.7) [n=11]	13 (65.0) [n=20]	1.000

CSF: cerebral spinal fluid; LMVV: large/medium vessel variant; SVV: small vessel variant; PCNSV: primary central nervous system vasculitis.
*Abnormal CSF is defined by either leukocyte counts >5 cells/mm^3 (pleocytosis) or protein level >45 mg/dl (elevated protein).

Brain images, CSF and brain biopsy findings in the LMVV patients

Table IV summarises the brain images and CSF findings in biopsy-proven and image-based PCNSV by affected vessel size. In the 11 LMVV cases, all biopsy-proven cases (n=4) showed contrast enhancement lesions on brain MRI, but only 1 case (14.4%) in 7 image-based PCNSV cases ($p=0.015$). Table V shows the detailed brain images, CSF, and brain biopsy findings in the 11 PCNSV patients with LMVV. Diagnosis of image-based PCNSV was made in seven patients (Case 1-7) according to the presence of CSF pleocytosis (Case 1-7) and strong/concentric VWE (Case 1-6: HR-VWI was not performed in case

Table IV. Brain images and CSF findings in biopsy-proven and image-based PCNSV by affected vessel size.

	LMVV (n=11)		*p* value	SVV (n=23)		*p* value
	Biopsy-proven (n=4)	Image-based (n=7)		Biopsy-proven (n=18)	Image-based (n=5)	
MRI findings, n (%)						
Brain infarcts	4 (100.0)	7 (100.0)	1.000	9 (50.0)	5 (100.0)	0.116
Parenchymal haemorrhage	1 (25.0)	0 (0.0)	0.364	5 (27.8)	0 (0.0)	0.545
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	1.000	2 (11.1)	2 (40.0)	0.194
White matter lesion	1 (25.0)	1 (14.3)	1.000	10 (55.6)	2 (40.0)	0.640
Tumour-like lesion	0 (0.0)	0 (0.0)	1.000	8 (44.4)	0 (0.0)	0.122
Contrast enhancement lesion	4 (100.0)	1 (14.3)	0.015	18 (100.0)	2 (40.0)	0.006
Arterial stenosis, n (%)						
Proximal segment	1 (25.0)	6 (85.7)	0.088	0 (0.0)	0 (0.0)	1.000
Middle segment	4 (100.0)	6 (85.7)	1.000	0 (0.0)	0 (0.0)	1.000
Smaller distal branch	4 (100.0)	6 (85.7)	1.000	3 (16.7)	5 (100.0)	0.002
None	0 (0.0)	0 (0.0)	1.000	16 (84.2)	0 (0.0)	0.002
HR-VWI findings, n (%)						
VWE	4 (100.0) [n=4]	6 (100.0) [n=6]	1.000	1 (11.1) [n=9]	1 (20.0) [n=5]	1.000
Strong/concentric VWE	3 (75.0) [n=4]	6 (100.0) [n=6]	0.400	1 (11.1) [n=9]	0 (0.0) [n=5]	1.000
Mild/eccentric VWE	1 (25.0) [n=4]	0 (0.0) [n=6]	1.000	0 (0.0) [n=9]	1 20.0) [n=5]	0.385
VWE score	9 (1-19) [n=4]	3 (2-13) [n=6]	0.914	0 (0-2) [n=9]	0 (0-0) [n=5]	0.943
CSF findings, n (%)						
Abnormal *	4 (100.0)	7 (100.0)	1.000	11 (73.3) [n=15]	5 (100.0) [n=5]	0.266
Pleocytosis*	3 (75.0)	7 (100.0)	0.364	9 (60.0) [n=15]	3 (60.0) [n=5]	1.000
Elevated protein*	3 (75.0)	5 (71.4.)	1.000	8 (53.3) [n=15]	5 (100.0) [n=5]	0.114

CSF: cerebral spinal fluid; PCNSV: primary central nervous system vasculitis; LMVV: large/medium vessel variant; SVV: small vessel variant; MRI: magnetic resonance image; HR-VWI: high-resolution vessel wall image; VWE: vessel wall enhancement. *Abnormal CSF is defined by either leukocyte counts >5 cells/mm^3 (pleocytosis) or protein level >45 mg/dl (elevated protein).

Table V. Brain images, CSF and biopsy findings in all LMVV patients.

Case no.	Diagnosis	MRI findings		Vessel involvement		HR-VWI		CSF findings		Brain biopsy
Age (y), sex		Pattern	CEL	MRA	DSA	VWE pattern	VWE score	WBC (cells/mm^3)	Protein (mg/dl)	
1/42/F	Image-based	BIs	None	P	P, S	SC	2	28	51	NO
2/47/F	Image-based	BIs, WML	None	M	M, S	SC	26	10	62	NO
3/49/F	Image-based	BIs	None	P, M	P, M	SC	4	6	26	NO
4/35/F	Image-based	BIs	Yes	P, M	P, M, S	SC	8	11	41	NO
5/53/F	Image-based	BIs	None	P, M, S	P, M, S	SC	2	11	93	Negative
6/33/M	Image-based	BIs	None	P, M, S	P, M, S	SC	2	58	89	Negative
7/63/M	Image-based	BIs	None	P, M	P, M,S	NO	-	13	75	Negative
8/27/M	Biopsy-proven	BIs	Yes	M	M, S	SC	2	13	45	Lymphocytic
9/57/M	Biopsy-proved	BIs, WML, PH	Yes	M	M, S	ME	1	1	48	Lymphocytic
10/53/F	Biopsy-proven	BIs	Yes	P, M, S	P, M, S	SC	16	133	87	Lymphocytic
11/46/M	Biopsy-proven	BIs	Yes	M	M, S	SC	20	16	70	Granulomatous

CSF: cerebral spinal fluid; LMVV: large/medium vessel variant; Bis: brain infarcts; PH: parenchymal haemorrhage; SAH: subarachnoid haemorrhage: WML: white matte lesion; TL: tumour-like lesion; CEL: contrast enhancement lesion; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; P: proximal segment; M: medium segment; S: smaller distal branch; HR-VWI: high-resolution vessel wall image; VWE: vessel wall enhancement; SC;:strong/concentric enhancement pattern; ME: mild/eccentric enhancement pattern; NO: not done.

7). Although seven patients underwent brain biopsy (Case 5-11), three patients (Case 5-7) failed to identify the inflammation of vessels in the brain tissue specimens. In biopsy negative cases, biopsy specimens were collected from the ischaemic lesions site without contrast enhancement (Case 5, Fig. 5 and Case 6) and random sampling of the non-dominant frontal lobe (Case 7).

Brain images, CSF and brain biopsy findings in the SVV patients

In the 23 SVV cases, contrast enhancement lesion was observed in all biopsy-proven cases (100.0%) and 2 of 5 patients (40.0%) in the image-based SVV patients (p=0.006) (Table IV). All image-based PCNSV with the SVV had brain infarcts, multi-vessel involvements in the smaller distal branch on DSA, and CSF abnormalities (Table IV). Table VI shows the detailed brain images, CSF, and brain biopsy findings in the 23 PCNSV patients with SVV. All image-based SVV patients did not conduct brain biopsy (Case 12-16). Although two of five image-based SVV patients (Case 12, 13) did not present CSF pleocytosis, the final diagnosis was made according to the presence of

Table VI. Brain images, CSF, and biopsy findings in all SVV patients.

Case no.	Diagnosis	MRI findings		Vessel involvement		HR-VWI		CSF findings		Brain biopsy
Age (y), sex		Pattern	CEL	MRA	DSA pattern	VWE score	VWE (cells/mm^3)	WBC (mg/dl)	Protein	
12/56/M	Image-based	BIs	None	None	S	None	0	1	78	NO
13/50/F	Image-based	BIs, WML	None	None	S	ME	3	2	122	NO
14/78/F	Image-based	BIs, WML, SAH	None	None	S	None	0	36	96	NO
15/48/M	Image-based	BIs	Yes	None	S	None	0	15	66	NO
16/48/M	Image-based	BIs, SAH	Yes	None	S	None	0	15	54	NO
17/57/M	Biopsy proven	BIs	Yes	None	S	None	0	96	74	Lymphocytic
18/36/M	Biopsy proven	BIs, WML,	Yes	None	S	None	0	195	113	Lymphocytic
19/49/F	Biopsy proven	BIs, WML	Yes	None	None	NO	-	3	35	Lymphocytic
20/65/M	Biopsy proven	BIs, TL, PH	Yes	None	None	None	0	3	61	Lymphocytic
21/65/F	Biopsy-proven	BIs	Yes	NO	None	NO	-	11	43	Lymphocytic
22/59/M	Biopsy proven	BIs, WML	Yes	None	NO	NO	-	20	127	Lymphocytic
23/52/M	Biopsy proved	BIs, PH	Yes	None	NO	NO	-	105	112	Lymphocytic
24/58/M	Biopsy proven	TL, WML	Yes	None	NO	NO	-	1	34	Lymphocytic
25/36/M	Biopsy proven	WML, PH, SAH	Yes	None	NO	NO	-	NO	NO	Lymphocytic
26/36/M	Biopsy proven	TL	Yes	NO	None	NO	-	NO	NO	Lymphocytic
27/45/M	Biopsy-proven	TL, WML	Yes	None	None	None	0	4	68	Lymphocytic
28/54/M	Biopsy proven	TL	Yes	None	NO	NO	-	1	17	Lymphocytic
29/19/M	Biopsy proven	BIs, SAH	Yes	None	S	SC	5	19	51	Necrotising
30/33/F	Biopsy proven	BIs, WML	Yes	None	NO	None	0	NO	NO	Necrotising
31/40/M	Biopsy proven	TL, WML, PH	Yes	None	None	None	0	2	26	Necrotising
32/36/F	Biopsy proven	TL	Yes	None	NO	None	0	7	36	Necrotising
33/43/M	Biopsy proven	TL, WML, PH	Yes	None	NO	None	0	16	44	Necrotising
34/71/F	Biopsy proven	WML	Yes	None	None	NO	-	37	139	Granulomatous

CSF: cerebral spinal fluid; SVV: large/medium vessel variant; Bis: cerebral infarcts; PH: parenchymal haemorrhage; SAH: subarachnoid haemorrhage; WML: white matte lesion; TL: tumour-like lesion; CEL: contrast enhancement lesion; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; P: proximal segment; M: medium segment; S: smaller distal branch; HR-VWI: high-resolution vessel wall image; VWE: vessel wall enhancement; SC: strong/concentric enhancement pattern; ME: mild/eccentric enhancement pattern; NO: not done.

high CSF protein level (case 12: 78mg/dl; Fig. 6, and Case 13: 122 mg/dl), DSA findings, and clinical pictures.

Discussion

LMVV patients had more likely to have brain infarcts and strong/concentric VWE than SVV patients. HR-VWI techniques have been developed to directly evaluate the arterial wall's affecting characteristics in intracranial vasculopathy (19-22). VWE patterns of the PCNSV typically represent thickening, smooth, concentric, and strong enhancement of the vessel wall (19-22). Eiden *et al*. (43) recently compared the 2D and 3D HR-VWI sequences in patients with suspected cerebral vasculitis. There were no significant differences in the diagnosis of cerebral vasculitis between the HR-VWI sequences (sensitivity: 67% on 2D and 3D. specificity; 44% on 2D and 48% on 3D). In the present study, strong/concentric VWE was identified in 37.5% (10/24) overall, 90.0% (9/10) for the LMVV, and 7.1% (1/14) for the SVV, respectively. Therefore, HR-VWI can be a useful diagnostic tool for evaluating vessel wall characteristics in PCNSV patients with LMVV. By contrast, the prevalence rate of strong/concentric VWE seems to be lower in SVV patients. The current HR-VWI technique has a limited capacity for evaluation of the smaller distal involvements beyond the spatial resolution (22). A previous study showed that none of VWE was observed in smaller distal branches on 2D and 3D HR-VWI sequences in intracranial vasculitis (43). Therefore, we diagnosed patients with smaller distal branch involvements in the cerebral vascular image as SVV. In this study, eight patients with smaller distal branch involvements underwent HR-VWI. Of these, only one patient had strong/concentric VWE on HR-VWI (Case 29). Larger samples are needed to confirm the accurate prevalence of strong/concentric VWE by affected vessel size and its clinical implications in PCNSV patients.

In the present study, approximately 80% of SVV patients underwent brain biopsy and the positive rate of brain biopsy was 100% in the SVV and 57.1% in the LMVV, respectively. Moreover, we also found that contrast enhancement lesion was more common in SVV than in LMVV. Despite advances in neuroimaging techniques, brain biopsy remains the gold standard for the diagnosis of PCNSV (37-39). The sensitivity of brain biopsy for the diagnosis of PCNSV was 57–63% in the previous retrospective analysis (8, 37-39). However, diagnostic accuracy increased to approximately 80% by targeting areas of imaging abnormality, while none of the untargeted biopsies showed vasculitis (37-39). The present study showed that all biopsy-proven cases had contrast parenchymal enhancement lesions which are accessible for surgery. Although biopsy from the non-dominant frontal lobe is recommended in patients without accessible lesions for surgery (39, 44), all biopsy-negative patients with LMVV (Case 5-7) showed no targeting contrast enhancement lesions in this study. Zeiler *et al*. (25) reported that the combination of HR-VWI and the reconstructed contrast-enhanced MRA and TOF MRA source images can be useful to identify

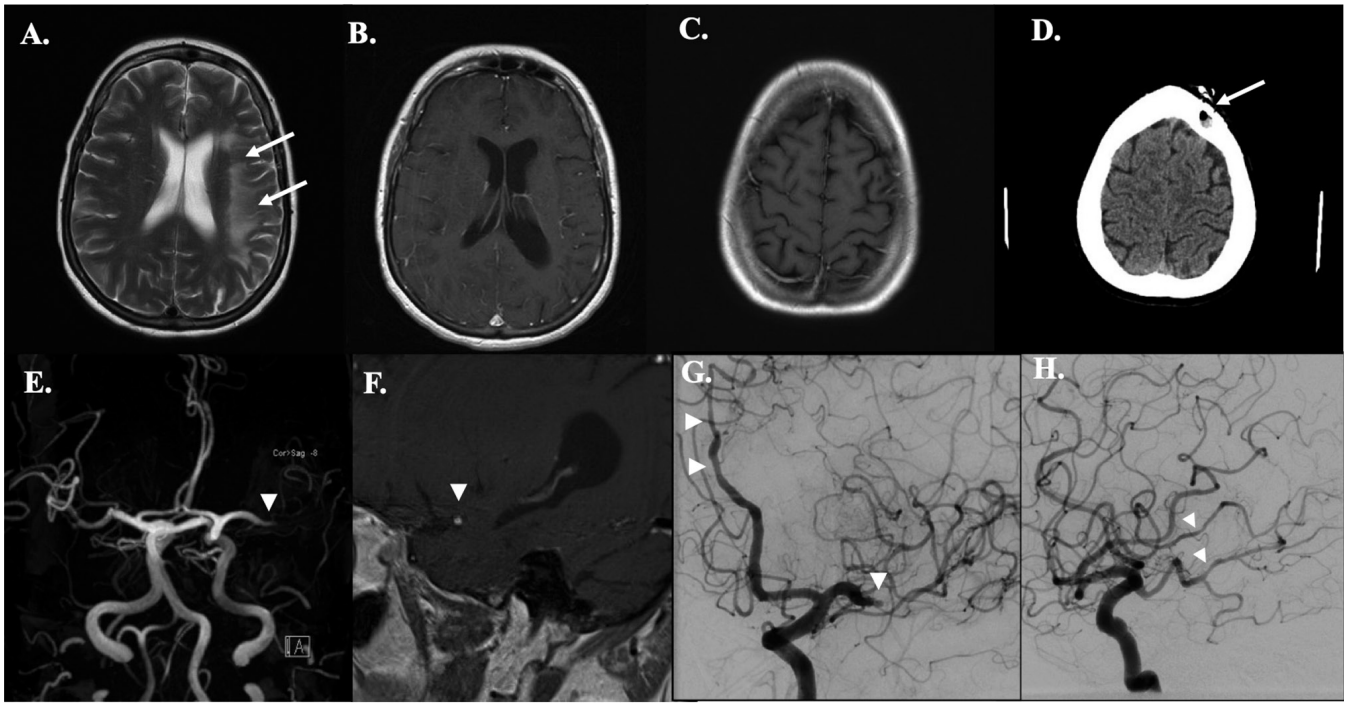

Fig. 5. Brain MRI showed no targeting enhancement lesion in the LMVV with inflammatory CSF profile (Case 5: image-based and biopsy negative).
A: Axial T2 weighted images showing subcortical infarction in the left MCA area (arrows).
B-**C**: Axial gadolinium-enhanced MRI demonstrating no enhancement lesion in the leptomeninges and brain parenchyma.
D: Brain biopsy was conducted from the left frontal lobe (arrow).
E: TOF-MRA revealing cut-off at the left M1 distal to M2 portion (arrowhead).
F: HR-VWI showing the strong and concentric vessel wall enhancement of the left M2 (arrowhead).
G: DSA showing the left M1 distal occlusion (arrowhead) and diffuse irregularity in the left A2 to A3 segment (arrowheads).
H: DSA showing the mild irregularity in the right distal MCA and PCA branch (arrowheads) at occlusion at the left M1 distal to M2 trunk.

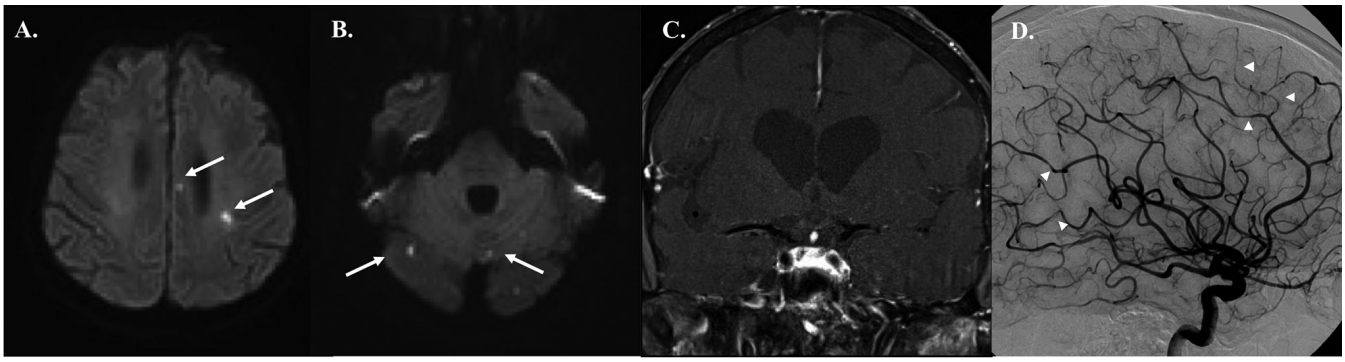

Fig. 6. Brain MRI and DSA showed multiple infarcts and vessel involvements in only smaller distal branches (Case 12: image-based).
A-**B**: Axial DWI showing small multiple territorial infarcts in anterior and posterior circulations (arrows).
C: Coronal HR-VWI demonstrating no enhancement lesion in the vessel wall, leptomeninges, and brain parenchyma.
D: DSA showing the diffuse irregularity in the right distal ACA and MCA branches (arrowheads).

the targeting of intracranial vessels for brain biopsy in PCNSV patients. Therefore, brain biopsy should be considered in suspected PCNSV patients with targeting contrast enhancement lesions. These imaging approaches might be helpful to discriminate candidates for brain biopsy and improve the diagnostic accuracy in patients with PCNSV.

Most of the PCNSV patients represented abnormal MRI findings including brain infarcts (54-81%), haemorrhagic complications (8-33%), leptomeningeal or parenchymal enhancement lesion (40-58%), and tumour-like lesion (6-15%) (8, 16-18). The differences in the prevalence rate for brain MRI characteristics can be explained by the size of the study cohorts, the proportion of biopsy-proven cases, imaging protocol, and timing for image evaluation. In the present study, approximately 65% of PCNSV patients were diagnosed by brain biopsy. In particular, the tumour-like lesion was identified only in SVV patients. The previous study reported that most patients with tumour-like presentation have a negative angiography, which suggests a preponderant small-vessel involvement (17, 31). The pathophysiology of the formation of a mass-like lesion has been speculated to be the result of a breakdown of the

blood-brain barrier of the small vessels via the infiltration of inflammatory cells in the perivascular and parenchymal regions (45). However, differentiation between tumour-like vasculitis and brain tumours including glioma and lymphoma is challenging because of similar MRI findings (46). Our results suggest that PCNSV should be considered as a differential diagnosis in patients presenting with tumefactive lesions of the CNS.

In the present study, five SVV patients (Case 12-16) were diagnosed with the image-based PCNSV based on abnormal CSF findings, multiple small distal branch involvements on the DSA, and clinical presentation. Our cohort demonstrated DSA in all image-based PCNSV to evaluate cerebral vasculature in detail. DSA is still considered the diagnostic modality of choice in detecting segmental narrowing or dilation, especially in more distal and small vessels (26, 27). However, the specificity of cerebral angiography for diagnosis of PCNSV is regarded as low and further workup to rule out other mimicking disorders is needed (26). In contrast to LMVV, SVV had a lower incidence of vessel wall enhancement lesions on the HR-VWI. Moreover, in patients without the parenchymal contrast enhancement lesion for brain biopsy (Case 12-14), the diagnosis should be given more carefully based on CSF abnormalities, DSA findings, and clinical pictures. To date, little is known about a diagnostic approach for image-based PCNSV with only smaller distal branch involvements. Although previous studies classified those patients as image-based LMVV (30-32), all image-based PCNSV patients conducted neither DSA nor CSF in these cohorts (30-32). Therefore, previous reports may have the potential that some image-based PCNSV have not been accurately diagnosed (30-32). Diagnosis of image-based PCNSV with smaller distal branches can be challenging due to the lack of clear evidence such as histological analysis and VWE on HR-VWI. Our eligibility criteria and angiographic classification might be useful to diagnose those patients as image-based PCNSV.

Differentiating PCNSV and RCVS can be challenging in the clinical setting because both conditions have polymorphic manifestations with many overlapping clinical and radiographic features including headaches, focal neurologic deficits, strokes, and angiographic abnormalities (5-8). An early distinction is particularly important to initiate immunosuppressive treatments for PCNSV, which may worsen clinical outcomes and radiographic abnormalities in RCVS (47). Scoring systems to distinguish RCVS from PCNSV and other intracranial vasculopathy during admission have been developed to better differentiate between these entities in the acute phase (6). By contrast, the long-term clinical and radiographic features seem to differ between these conditions. PCNSV has been considered as a relapsing-remitting disease with a heterogeneous disease course and relapse affected approximately 30-50% of PCNSV patients under immunosuppressive treatments (48-50). In this study, relapse was observed in 32.4% of PCNSV patients during the follow-up (median time of 1.6 years). Repeated clinical, CSF, and neuroimaging can be informative to assess the disease activity through the management of patients with PCNSV (1, 2, 21, 23, 24). HR-VWI has the potential to provide supplemental information to assess response to therapy in PCNSV (20, 23, 24). Improving the total VWE score may indicate a good response to treatment in PCNSV, while relapse patients might have temporal VWE score worsening during the clinical course (23). On the other hand, RCVS typically follows a monophasic benign self-limiting course (51). Most patients experience resolution of headache within 4 weeks and angiographic findings 3 months after clinical onset (51). A long-term follow-up study has been undertaken in a large Taiwanese RCVS cohort (n=168). Nine (5.4%) developed recurrent RCVS, which occurred between 6-87 months after the initial episode (52). Considering the patient's overall clinical picture, radiographic features, and CSF findings in both acute and chronic phases may be the most effective way of differentiating these two entities.

The present study has several limitations. First, this study was conducted at a single centre, and the number of PCNSV was relatively small. Second, the diagnostic approaches including CSF analysis, DSA, HR-VWI, and brain biopsy were decided based on the attending physician's judgments. Therefore, there have been missing data and selection and referral biases that we cannot control. Third, the prevalence of granulomatous vasculitis was low (9.1%) in biopsy-proven PCNSV compared to previous report (37). By contrast, lymphocytic vasculitis (68.2%) was the most frequently observed in our cohort. De Boysson *et al*. (17) reported that eight of nine patients with tumour-like presentation (89%) showed lymphocytic vasculitis, while granulomatous vasculitis was observed in one patient. In the present study, five of eight patients with tumour-like presentation showed lymphocytic vasculitis. SVV presented a wide range of brain MRI abnormalities including brain infarcts, white matter lesions, tumour-like lesions, and parenchymal enhancements. Therefore, histopathological findings may be influenced by the variation of brain MRI abnormalities. Finally, the median interval between symptom onset and registration was 1.3 years. Indeed, about 30% of PCNSV patients were registered in the chronic phase. The prevalence of brain MRI abnormalities might be influenced by the disease activities and timing for evaluation. Despite these limitations, the strengths of this study compared to the previous study are as follows:1) prospective registration, 2) CSF analysis and DSA were demonstrated in all patients with the image-based PCNSV, and 3) presentation of detailed neuroimaging, CSF, and brain biopsy findings in all PCNSV patients. Large prospective collaborative studies are required to reach more definitive conclusions about clinical characteristics, brain MRI, and pathological findings by affected vessel size.

The diagnostic approaches for PCNSV differ concerning the affected vessel size. In LMVV patients, the diagnosis of PCNSV was mainly based on the evidence of strong/concentric VWE

on HR-VWI. By contrast, brain biopsy should be considered in suspected PCNSV patients with SVV if a parenchymal enhancement lesion is detected. In patients without VWE on HR-VWI and targeting contrast enhancement lesions, careful assessments including CSF abnormalities, DSA findings, and clinical pictures are needed for the diagnosis of PCNSV.

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