Journal of Neurology (2019) 266:1708–1715
https://doi.org/10.1007/s00415-019-09318-9

ORIGINAL COMMUNICATION

Occurrence of cerebral small vessel disease at diagnosis of MPO-ANCA-associated vasculitis

Hiroki Tani[1] · Koji Nagai[2] · Takafumi Hosokawa[1] · Kenichiro Hata[2] · Takuya Kotani[2] · Shimon Ishida[1] · Tohru Takeuchi[2] · Shigeki Arawaka[1]

Received: 15 February 2019 / Revised: 7 April 2019 / Accepted: 9 April 2019 / Published online: 13 April 2019

Abstract

Background Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) often causes peripheral nervous system impairments. However, little is known about subclinical involvements of the central nervous system in AAV. We investigated the frequency and progression of cerebral small vessel disease (SVD) in patients with AAV.

Methods This single-center, case–control study comprised 56 patients with myeloperoxidase (MPO)-ANCA-positive AAV. Cerebral SVD presenting periventricular and deep white matter hyperintensities was assessed using brain magnetic resonance imaging (MRI). Seventy-five patients with non-stroke-associated neurological diseases were employed as controls.

Results At clinical diagnosis of MPO-ANCA-positive AAV, the frequency of periventricular hyperintensities in the AAV group was significantly higher than that in the control group ($P=0.014$). Shinohara and Fazekas grades of periventricular hyperintensities in the AAV group were significantly higher than those in the control group ($P=0.019$ and 0.020, respectively). In the AAV group, atherosclerosis-related factors, such as age and hypertension, were not associated with the Shinohara grades of periventricular hyperintensities, whereas serum CRP levels were significantly associated (odds ratio = 6.000, 95% confidence interval 1.648–21.840, $P=0.004$). MRI changes were followed in 23 patients with AAV until 2 years after 6 months of diagnosis. Six of these patients worsened the grades of periventricular hyperintensities, while two of 27 in the control group worsened the grades ($P=0.013$).

Conclusion Inflammatory events are associated with the occurrence of cerebral SVD before clinical diagnosis of MPO-ANCA-positive AAV. The patients may be continuously exposed to the risk of cerebral SVD after immunosuppressive therapy.

Keywords Small vessel disease · Vasculitis · MPO-ANCA · C-reactive protein

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a primary vasculitic disease pathologically characterized by inflammation of the small and medium-sized vessels of the body [1]. More than ten types of neutrophil granule-containing substances have been identified as ANCA antigens. Among them, myeloperoxidase (MPO) and proteinase 3 (PR3) are strongly related to diagnosis and pathogenesis of AAV [2]. It is proposed that classification according to the type of ANCA is useful for understanding the clinical features and genetic background of AAV [3]. In addition, the reactivity with immunosuppressive therapy is dependent on the type of ANCA, and the recurrence rate in PR3-ANCA-positive AAV is significantly higher than that in MPO-ANCA-positive AAV [4–6].

ANCA-associated vasculitis often causes peripheral nervous system impairments [7]. Generally, MPA and EGPA cause central nervous system impairments much less frequently than peripheral neuropathy [7–9]. 7–11% patients with GPA are shown to cause central nervous system impairments [10]. However, it is unclear as to the subclinical involvement of the central nervous system in AAV. To address this issue, we focused on periventricular and deep

✉ Shigeki Arawaka
sarawaka@osaka-med.ac.jp

[1] Division of Neurology, Department of Internal Medicine IV, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

[2] Division of Rheumatology, Department of Internal Medicine IV, Osaka Medical College, Osaka, Japan

white matter hyperintensities on T2- and FLAIR-weighted magnetic resonance imaging (MRI) as cerebral small vessel disease (SVD) in MPO-ANCA-positive AAV and assessed the frequency and progression of cerebral SVD. Here, we report the association of MPO-ANCA-positive AAV with subclinical occurrence of cerebral SVD.

Methods

Subjects

The subjects of this study were 97 patients with AAV who were serially admitted to Osaka Medical College Hospital between January 2013 and October 2018. All patients were newly diagnosed as AAV according to the EMEA algorithm [11] and had received no immunosuppressive treatments elsewhere. Among the patients with AAV, 74 underwent brain MRI at clinical diagnosis of AAV before starting immunosuppressive therapy to assess the central nervous system involvements despite the presence and absence of neurological symptoms. They included 53 with MPO-ANCA-positive AAV, 8 with PR3-ANCA-positive AAV, 3 with ANCA-double positive AAV and 10 with ANCA-negative AAV (Fig. 1). In this study, 56 patients were enrolled as MPO-ANCA-positive AAV. They were classified into 7 with EGPA, 19 with GPA, 25 with MPA and 5 with unclassifiable AAV.

As a control group, there were 75 patients with non-stroke-associated neurological and neuromuscular junction diseases. They serially came to our hospital during the same period and included 11 with myasthenia gravis, 8 with Guillain–Barré syndrome, 5 with chronic inflammatory demyelinating polyneuropathy, 4 with multifocal motor neuropathy, 17 with Parkinson's disease, 11 with amyotrophic lateral sclerosis and 19 with spinocerebellar degeneration. In these patients, brain MRI was performed to differentiate the organic brain abnormalities. Clinical information of the patients was collected from the medical records.

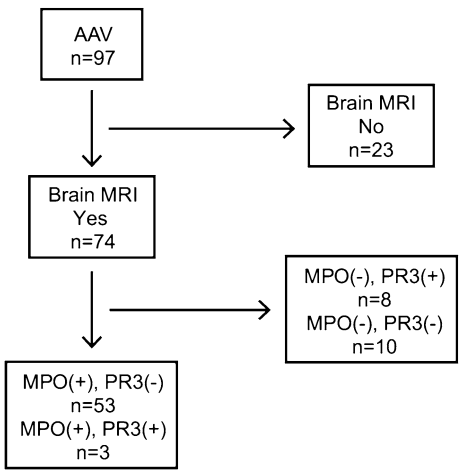

Fig. 1 Flowchart of this study. 74 of 97 patients with AAV underwent brain MRI. Of these patients, 56 patients with MPO-ANCA-positive AAV were enrolled in this study. As the control group, 75 patients with non-stroke-associated neurological and neuromuscular junction diseases were employed

Clinical findings and laboratory examinations

Information on age at diagnosis, sex, smoking status, and the presence of diabetes mellitus, hypertension and dyslipidemia was collected. Smoking status was evaluated by the Brinkman index. The presence of diabetes mellitus, hypertension and dyslipidemia was first checked by the medical history or by laboratory examinations on admission. Diabetes mellitus was judged according to World Health Organization criteria [12] or by current medication. Hypertension was defined as resting blood pressure ≥ 140/90 mmHg or by current use of antihypertensive agents. Dyslipidemia was defined as low-density lipoprotein cholesterol levels ≥ 160 mg/dL or triglyceride levels ≥ 150 mg/dL [13] or by current medication. For assessment of disease activity for AAV, serum CRP levels, serum MPO-ANCA titers and Birmingham Vasculitis Activity Score (BVAS version 3) just before starting the treatment were used [14, 15]. Serum MPO-ANCA was measured by the CLEIA method. BVAS is an index to assess the disease activity of systemic vasculitis by scoring five systemic symptoms and symptoms of eight organs [14, 15].

Assessment of cerebral SVD on brain MRI

Diffusion-, T2- and FLAIR-weighted images at 2-mm slices and MR angiography were performed on 3.0T MRI (GE Signa HDxt). For assessment of periventricular and deep white matter hyperintensities at baseline, T2- and FLAIR-weighted transverse images entirely covering the bodies of the lateral ventricles were used at diagnosis of AAV. The grades of periventricular and deep white matter hyperintensities were assessed by the Shinohara classification with minor modification and Fazekas scale (Table 1) [16, 17]. For assessment of the progression of periventricular and deep white matter hyperintensities, follow-up MRI images until 2 years after onset were analyzed in 44 MPO-ANCA-positive AAV patients and 39 patients in the control group. Clinical information was collected by K. N., and the assessment of MRI was performed by H. T. blind to the diagnosis and clinical information. We did not find patients with severe sclerotic changes in the internal carotid, middle cerebral, vertebral and basilar arteries on MR angiography in the AAV and control groups.

Table 1 Shinohara classification and Fazekas scale of periventricular and deep white matter hyperintensities on brain MRI

	Shinohara classification	Fazekas scale
Periventricular hyperintensities		
Grade 0	Absence or periventricular "rim" only	Absence
Grade 1	Localized lesions like "caps"	"Caps" or pencil-thin lining
Grade 2	Extended along the whole periventricular area	Smooth "halo"
Grade 3	Irregular PVH extending into the deep white matter	Irregular PVH extending into the deep white matter
Grade 4	Extending throughout deep and subcortical white matter	–
Deep white matter hyperintensities		
Grade 0	Absence	Absence
Grade 1	Punctate foci (diameter < 3 mm) or dilatation of perivascular spaces	Punctate foci
Grade 2	Patchy foci (diameter ≥ 3 mm)	Beginning confluence of foci
Grade 3	Confluent foci in deep white matter	Large confluent areas
Grade 4	Confluence widely distributed in most white matter	–

PVH periventricular hyperintensity

Statistical analysis

To compare categorical and continuous variables between groups, Pearson's Chi square test and Student's *t* test were used. Frequency of cerebral SVD was assessed by Pearson's Chi square test. Comparison of the grades of periventricular hyperintensities between groups was performed by Student's *t* test. To analyze independent contributing factors for cerebral SVD, a linear logistic regression analysis was used. Analysis for rates of progressive SVD cases was performed by the Kaplan–Meier method and differences between survival curves were assessed by the log-rank test. The values of each factor were expressed as mean ± standard deviation, and P value < 0.05 was considered statistically significant. Statistical analysis was performed using JMP Pro 13 software (SAS Institute Inc., Cary, NC, USA).

Data availability

All data analyzed during this study are included in this article.

Results

Comparison of demographic data between MPO-ANCA-positive AAV and control groups

Patient profiles are summarized in Table 2. The mean age of the AAV group was 74.6 ± 9.6 years old, while that of the control group was 72.0 ± 9.2 years old. There was no significant difference in the mean age between the two groups. The rates of men were comparable between the two groups. There were no significant differences in the rates of patients with hypertension, diabetes mellitus and dyslipidemia. Additionally, the Brinkman index for smoking status showed no significant difference between the two groups. The levels of serum CRP in the MPO-ANCA-positive AAV group (8.6 ± 0.9 mg/dL) were significantly higher than those in the control group (0.2 ± 0.1 mg/dL, P < 0.001). These findings showed that general risk factors for atherosclerosis were comparable between the two groups, whereas inflammation occurred in the MPO-ANCA-positive AAV group at clinical diagnosis.

Table 2 Comparison of demographic data between MPO-ANCA-positive AAV and control groups

	AAV (n = 56)	Control (n = 75)	P value
Age	74.6 ± 9.6	72.0 ± 9.2	0.128
Men, *n* (%)	25/56 (44.6%)	35/75 (46.7%)	0.818
Diabetes mellitus, *n* (%)	14/56 (25.0%)	16/75 (21.3%)	0.241
Hypertension, *n* (%)	22/56 (39.3%)	26/75 (34.7%)	0.588
Dyslipidemia, *n* (%)	14/56 (25%)	19/75 (25.3%)	0.965
Smoking (Brinkman index)	216.7 ± 54.8	194.6 ± 42.2	0.782
ANCA titer (IU/mL)	184 ± 37.6	–	–
CRP (mg/dL)	8.6 ± 0.9	0.2 ± 0.1	< 0.001
BVAS	18.0 ± 7.5	–	–

Data are expressed as mean ± standard deviation or *n* (%)

ANCA, anti-neutrophil cytoplasmic antibody; CRP, C-reactive protein; BVAS, Birmingham Vasculitis Activity Score

Frequency of cerebral SVD at clinical diagnosis of MPO-ANCA-positive AAV

On brain MRI, 11 of 56 patients (19.6%) with MPO-ANCA-positive AAV showed acute and subacute

symptomatic lesions: 6 with acute cerebral infarction (10.7%) that was observed as the presence of high intensities on diffusion-weighted images, 1 with cerebral hemorrhage (1.8%), 1 with subarachnoid hemorrhage (1.8%) and 3 with hypertrophic pachymeningitis (5.4%) (Table 3). Acute and subacute intracranial lesions were not seen in the control group. In the brain stem, cerebellum, and cortical and subcortical areas of the cerebrum, a total of 21 of 56 patients (37.5%) with MPO-ANCA-positive AAV showed chronic ischemic changes observed as high intensities on T2- and FLAIR-weighted images and iso-intensity on diffusion-weighted images. Distribution of these changes was 11 of the frontal lobe, 3 of the temporal lobe, 4 of the parietal lobe, 2 of the occipital lobe, 4 of the brainstem and 3 of the cerebellum. In the control group, 23 of 75 patients (30.7%) showed chronic ischemic changes. Distribution of these changes was ten of the frontal lobe, five of the temporal lobe, four of the parietal lobe, three of the occipital lobe, three of the brainstem and four of the cerebellum. There was no significant difference in the frequency of these chronic ischemic changes between the two groups ($P=0.724$).

Afterwards, to clarify cerebral SVD in MPO-ANCA-positive AAV at baseline, we examined the frequency of periventricular and deep white matter hyperintensities on T2- and FLAIR-weighted images at clinical diagnosis of AAV (Table 3). In the MPO-ANCA-positive AAV group, periventricular hyperintensities were seen in 49 (87.5%) of 56 patients. In the control group, they were seen in 52 (69.3%) of 75 patients. The frequency of periventricular hyperintensities in the MPO-ANCA-positive AAV group was significantly higher than that of the control group ($P=0.014$). We then compared the grades of periventricular hyperintensities according to the Shinohara classification (PVH) and the Fazekas scale (PVWM) (Table 3). The PVH grades in the MPO-ANCA-positive AAV group (mean ± standard deviation, 1.64 ± 1.09) were significantly higher than those in the control group (1.20 ± 1.03, $P=0.019$). Similarly, the PVWM grades in the MPO-ANCA-positive AAV group (1.57 ± 0.95) were significantly higher than those in the control group

Table 3 Comparison of cerebral SVD between MPO-ANCA-positive AAV and control groups

	AAV ($n=56$)	Control ($n=75$)	P value
Symptomatic lesions	11/56 (19.6%)	0/75 (0%)	–
Periventricular hyperintensities	49/56 (87.5%)	52/75 (69.3%)	0.014[a]
PVH (Shinohara classification)			
Grade 0	7 (12.5%)	23 (30.7%)	0.019[b]
Grade 1	21 (37.5%)	22 (29.3%)	
Grade 2	17 (30.4%)	24 (32.0%)	
Grade 3	7 (12.5%)	4 (5.3%)	
Grade 4	4 (7.1%)	2 (2.7%)	
PVWM (Fazekas scale)			
Grade 0	7 (12.5%)	23 (30.7%)	0.020[b]
Grade 1	21 (37.5%)	22 (29.3%)	
Grade 2	17 (30.4%)	24 (32.0%)	
Grade 3	11 (19.6%)	6 (8.0%)	
Deep white matter hyperintensities	47/56 (83.9%)	60/75 (80.0%)	0.563[a]
DSWMH (Shinohara classification)			
Grade 0	9 (16.1%)	15 (20.0%)	0.134[b]
Grade 1	16 (28.6%)	27 (36%)	
Grade 2	14 (25.0%)	17 (22.7%)	
Grade 3	12 (21.4%)	14 (18.7%)	
Grade 4	5 (8.9%)	2 (2.7%)	
DWM (Fazekas scale)			
Grade 0	9 (16.1%)	15 (20.0%)	0.196[b]
Grade 1	16 (28.6%)	27 (36%)	
Grade 2	14 (25.0%)	17 (22.7%)	
Grade 3	17 (30.4%)	16 (21.3%)	

Data are expressed as *n* (%)

PVH, periventricular hyperintensity; PVWM, periventricular white matter; DSWMH, deep and subcortical white matter hyperintensity; DWM, deep white matter

[a] and [b] indicate Pearson's Chi square test and Student's *t* test, respectively

(1.17 ± 0.96, $P = 0.020$). In contrast, there was no difference in the frequency of deep white matter hyperintensities between the two groups (83.9% in the MPO-ANCA-positive AAV group vs 80% in the control group, $P = 0.563$). The DSWMH grades of the Shinohara classification showed no difference between the MPO-ANCA-positive AAV group (1.79 ± 1.22) and the control group (1.48 ± 1.09, $P = 0.134$). The DWM grades of the Fazekas scale also showed no difference between the MPO-ANCA-positive AAV group (1.70 ± 1.08) and the control group (1.45 ± 1.04, $P = 0.196$).

Assessment of atherosclerosis and inflammatory risk factors for cerebral SVD at clinical diagnosis of MPO-ANCA-positive AAV

To clarify how MPO-ANCA-positive AAV affects the occurrence of cerebral SVD at clinical diagnosis of AAV, we analyzed the association of risk factors with the PVH grades in MPO-ANCA-positive AAV. In the univariable analysis, we assessed nine factors related to atherosclerosis and inflammation (Table 4). Atherosclerosis-related factors, such as age at diagnosis, the rate of men, hypertension, diabetes mellitus, dyslipidemia and smoking, were not associated with the PVH grades. Serum CRP levels were significantly associated with PVH grades [odds ratio (OR) 6.000, 95% confidence interval (CI) 1.648–21.840, $P = 0.004$], whereas ANCA titers (OR 0.515, 95% CI 0.164–1.616, $P = 0.251$) and BVAS values (OR 0.800, 95% CI 0.259–2.468, $P = 0.697$) were not associated with PVH grades. In the multivariable analysis, we assessed five factors related to atherosclerosis and inflammation. Atherosclerosis-related factors, such as age at diagnosis, the rate of men, and dyslipidemia, were not associated with the PVH grades. Serum CRP levels were significantly associated with PVH grades (OR 5.744, 95% CI 1.430–23.074, $P = 0.014$), whereas ANCA titers (OR 0.438, 95% CI 0.114–1.687, $P = 0.230$) were not associated.

Progression of cerebral SVD after clinical diagnosis of MPO-ANCA-positive AAV

To assess whether patients with MPO-ANCA-positive AAV continuously have the risk of cerebral SVD after introducing immunosuppressive therapy, we analyzed second brain MRI images of patients with MPO-ANCA-positive AAV until 2 years after diagnosis. 21 of the MPO-ANCA-positive AAV group and 12 of the control group underwent a second brain MRI within 6 months after diagnosis. In these patients, there were no significant changes in the PVH and PVWM grades for periventricular hyperintensities as compared with the grades at baseline. 23 of the MPO-ANCA-positive AAV

Table 4 Analysis of risk factors for periventricular hyperintensities in MPO-ANCA-positive AAV

Parameters	Univariate logistic regression model			
	OR	95% CI		*P* value
		Lower	Higher	
Age	2.404	0.764	7.562	0.131
Men	0.500	0.155	1.608	0.238
DM	2.037	0.490	8.462	0.309
HT	0.729	0.233	2.279	0.588
DL	3.692	0.730	18.682	0.082
Smoking	0.929	0.264	3.271	0.908
BVAS	0.800	0.259	2.468	0.697
ANCA	0.515	0.164	1.616	0.251
CRP	6.000	1.648	21.840	0.004
Parameters	Multivariate logistic regression model			
	OR	95% CI		*P* value
		Lower	Higher	
Age	2.120	0.568	7.910	0.264
Men	0.489	0.128	1.861	0.294
DL	3.128	0.532	18.381	0.207
ANCA	0.438	0.114	1.687	0.230
CRP	5.744	1.430	23.074	0.014

OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HT, hypertension; DL, dyslipidemia; BVAS, Birmingham Vasculitis Activity Score; ANCA, anti-neutrophil cytoplasmic antibody; CRP, C-reactive protein

group and 27 of the control group underwent a second brain MRI after 6 months of diagnosis. A total of 6 of 23 (26.1%) patients with MPO-ANCA-positive AAV worsened by one grade in PVH and PVWM scales, whereas 2 of 27 (7.4%) patients in the control group worsened by one grade in PVH and PVWM scales (Fig. 2). The progression of periventricular hyperintensities in the MPO-ANCA-positive AAV group was observed more frequently than that in the control group ($P=0.013$). There were no clear trends in age, sex, smoking, the grades of PVH, and ANCA titers at clinical diagnosis between the progressive and non-progressive groups in patients with MPO-ANCA-positive AAV (Table 5). Additionally, serum CRP levels were variable in the two groups.

Discussion

Cerebral SVD encompasses the pathological processes that affect the small arteries, venules, and capillaries of the brain, consequently presenting lacunar infarcts in the subcortical and white matter areas, large hemorrhages and microbleeds. Cerebral SVD is proposed to be classified into six subgroups by various etiologies: type 1 is arteriolosclerosis as age-related and vascular risk-factor-related SVD; type 2 is sporadic and hereditary cerebral amyloid angiopathy; type 3 is inherited or genetic SVD distinct from cerebral amyloid angiopathy; type 4 is inflammatory and immunologically

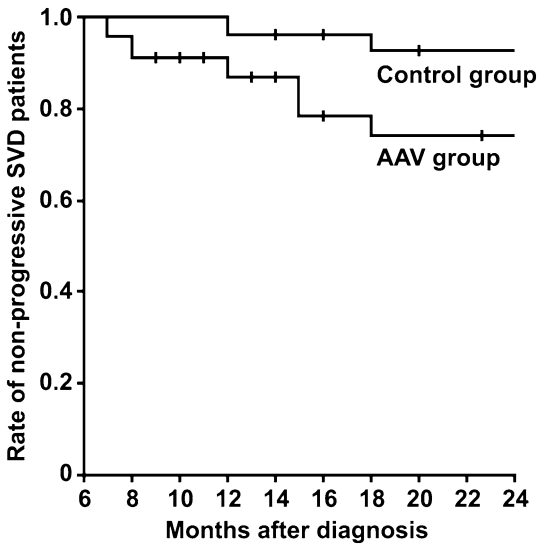

Fig. 2 Progression of periventricular hyperintensities in patients with MPO-ANCA-positive AAV. 23 patients with MPO-ANCA-positive AAV and 27 patients with non-stroke-associated disease control underwent follow-up brain MRI after 6 months of diagnosis. The follow-up period was 2 years. The graph shows the Kaplan–Meier curve for rate of non-progressive cerebral SVD patients in the PVH grades of the Shinohara classification. The data were analyzed by the log-rank test

mediated SVD, type 5 is venous collagenosis; and type 6 is other SVD [18]. According to this classification, we hypothesized that AAV highly contributed to cerebral SVD through inflammatory damage to the small vessels in the brain. However, it is unclear as to the pathological impact of AAV on cerebral SVD because clinical attention has not been paid to the involvement of cerebral SVD in AAV. In this study, to elucidate the frequency of cerebral SVD in patients with AAV, we analyzed the relationship of periventricular and deep white matter hyperintensities in MPO-ANCA-positive AAV. We found that the frequency of periventricular hyperintensities, but not deep white matter hyperintensities, was significantly higher at initial diagnosis in MPO-ANCA-positive AAV than in the control group. Additionally, the grades of periventricular hyperintensities expressing as PVH in the Shinohara classification and PVWM in the Fazekas scale were significantly higher in MPO-ANCA-positive AAV than those in the control group. These findings showed that MPO-ANCA-positive AAV was associated with subclinical occurrence of cerebral SVD.

To address the mechanism of cerebral SVD in MPO-ANCA-positive AAV, we assessed the risk factors related to arteriosclerosis or inflammation. There were no differences in risk factors related to arteriosclerosis, such as age at diagnosis, smoking, hypertension, diabetes mellitus and dyslipidemia, between the MPO-ANCA-positive AAV and control groups, and these risk factors were not associated with the grades of periventricular hyperintensities in MPO-ANCA-positive AAV. We found that serum CRP levels were significantly associated with PVH grades in MPO-ANCA-positive AAV at initial diagnosis. These data suggested that inflammatory processes were involved in cerebral SVD before clinical diagnosis of MPO-ANCA-positive AAV. In support of this idea, previous studies indicated that higher CRP levels were associated with the presence of cerebral SVD in older adults, and serum CRP was a sensitive systemic marker of inflammation in cerebral SVD [19, 20]. However, in older adults, higher CRP levels are considered to reflect the inflammatory endothelial damage of atherosclerotic processes in cerebral SVD. In MPO-ANCA-positive AAV, higher CRP levels may primarily reflect vasculitic endothelial damage because the frequency and grades of periventricular hyperintensities were statistically independent of atherosclerosis-related risk factors.

We also found that patients with MPO-ANCA-positive AAV showed progression of periventricular hyperintensities, although this analysis was based on a small population. This finding suggested that patients with MPO-ANCA-positive AAV may be continuously exposed to the risk of cerebral SVD after immunosuppressive therapy. However, we did not find the association of serum CRP levels at clinical diagnosis with the progression of periventricular hyperintensities. One may speculate that unknown factors other than CRP

Table 5 Clinical and demographic data at diagnosis in brain MRI follow-up patients with MPO-ANCA-positive AAV

Patient #	EMEA	Age	Sex	DM	HT	DL	Smoking	BVAS	ANCA	CRP	PVH
PVH progressive AAV group											
#1	MPA	79	F	+	+	+	0	14	289.0	9.60	1
#2	[a]	78	M	−	−	−	400	10	55.0	10.87	3
#3	GPA	75	F	−	−	−	0	27	229.0	0.03	2
#4	MPA	74	M	+	−	−	0	29	300.0	0.08	0
#5	EGPA	64	F	−	−	−	0	27	137.0	0.00	2
#6	GPA	79	M	−	+	−	0	31	113.0	3.01	0
PVH non-progressive AAV group											
#7	EGPA	79	F	−	−	−	0	13	40.9	5.15	2
#8	GPA	73	F	−	−	−	0	33	223.0	2.49	2
#9	GPA	82	M	−	−	−	800	8	101.0	14.74	3
#10	MPA	72	M	−	−	−	1600	22	1950	12.24	3
#11	MPA	89	M	−	−	−	0	15	3.5	1.13	1
#12	EGPA	54	M	−	+	+	480	24	550.0	1.80	1
#13	EGPA	49	M	−	−	−	220	25	11.5	6.12	1
#14	EGPA	50	F	−	−	−	0	11	4.1	1.43	1
#15	EGPA	61	M	+	+	−	400	25	133.0	2.28	2
#16	GPA	86	M	+	−	+	1040	18	125.0	16.94	2
#17	GPA	68	F	−	−	+	0	15	70.3	22.78	2
#18	[a]	70	F	−	−	−	0	11	166.0	4.57	0
#19	MPA	74	M	+	+	+	0	29	300.0	0.21	4
#20	GPA	81	F	−	−	−	300	20	90.1	11.63	2
#21	GPA	74	F	−	−	−	0	17	82.2	0.12	1
#22	GPA	73	F	−	−	−	0	30	384.0	0.06	0
#23	MPA	74	M	−	−	−	0	16	262.0	0.04	0

In the columns, + and − mean the presence and absence of disease, respectively. Smoking represents the Brinkman index. ANCA and CRP show MPO-ANCA titers (IU/mL) and values (mg/dL), respectively. PVH expresses the grades

EMEA, European Medicines Agency algorithm; DM, diabetes mellitus; HT, hypertension; DL, dyslipidemia; BVAS, Birmingham Vasculitis Activity Score; ANCA, anti-neutrophil cytoplasmic antibody; CRP, C-reactive protein. PVH, periventricular hyperintensity; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; F, female; M, male

[a]Unclassifiable AAV on EMEA

could affect the progression of cerebral SVD. Alternatively, a slight increase in serum CRP levels may be associated with the progression of cerebral SVD. Further studies using the larger cohort and more detailed follow-up dataset of serum CRP are necessary to reduce an introduction of uncontrolled bias and elucidate whether vasculitic changes affect the progression of cerebral SVD in MPO-ANCA-positive AAV.

Cerebral SVD is considered to associate with an increased risk of stroke, cognitive decline and depression in older adults [19]. Cerebral SVD precedes cerebral infarction in 60–70% of patients [16] and is related to the onset and recurrence of cerebral infarction [21]. Reciprocally, cerebral infarction patients have been shown to have cerebral SVD 10–20 years before the onset of cerebral infarction [22]. The results of this study showed that patients with MPO-ANCA-positive AAV were the latent high-risk group of cerebral SVD. In general, patients with AAV experience nonspecific symptoms, including fever, fatigue, appetite loss, weight loss, myalgia and joint pain, before being diagnosed by vasculitis-specific symptoms of organs [23]. These preclinical symptoms continue a few weeks or months [23]. In EGPA, patients have bronchial asthma for a few years before clinical diagnosis [24]. Although it is unclear when the elevation of serum CRP levels starts before clinical diagnosis, small vessel damage seems to occur silently in MPO-ANCA-positive AAV. In addition, patients with MPO-ANCA-positive AAV may be continuously exposed to the risk of cerebral SVD after immunosuppressive therapy. Accumulating data for cognitive decline and the occurrence of cerebral infarction would provide important insights into understanding the influence of cerebral SVD on the activities of daily living in patients with MPO-ANCA-positive AAV.

It should be noted that the present results were obtained from a single-center and case–control study. To validate

the results, it is necessary to accumulate the data by prospective analysis in a multi-center study. Additionally, to clarify the association of MPO-ANCA-positive AAV with cerebral SVD, assessment of cerebral microbleeds using T2*-weighted MRI would be useful.

Funding No targeted funding reported.

Compliance with ethical standards

Conflicts of interest The authors report no disclosures relevant to the manuscript.

Ethical standard This study was conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Ethics Committee of the Medical Faculty, Osaka Medical College (approval no. 2342).

References

1. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, Hellmich B, Holle JU, Laudien M, Little MA, Luqmani RA, Mahr A, Merkel PA, Mills J, Mooney J, Segelmark M, Tesar V, Westman K, Vaglio A, Yalçındağ N, Jayne DR, Mukhtyar C (2016) EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 75:1583–1594
2. Kallenberg CG (2014) Key advances in the clinical approach to ANCA-associated vasculitis. Nat Rev Rheumatol 10:484–493
3. Millet A, Pederzoli-Ribeil M, Guillevin L, Witko-Sarsat V, Mouthon L (2013) Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group? Ann Rheum Dis 72:1273–1279
4. Unizony S, Villarreal M, Miloslavsky EM, Lu N, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CM, St Clair EW, Ikle D, Tchao NK, Ding L, Brunetta P, Choi HK, Monach PA, Fervenza F, Stone JH, Specks U, RAVE-ITN Research Group (2016) Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. Ann Rheum Dis 75:1166–1169
5. Walsh M, Flossmann O, Berden A, Westman K, Höglund P, Stegeman C, Jayne D, European Vasculitis Study Group (2012) Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 64:542–548
6. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, Nachman PH, Jennette JC, Falk RJ (2012) Classification of antineutrophil cytoplasmic autoantibody vasculitis: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 64:3452–3462
7. Jennette JC, Falk RJ (1997) Small-vessel vasculitis. N Engl J Med 337:1512–1523
8. Cattaneo L, Chierici E, Pavone L, Grasselli C, Manganelli P, Buzio C, Pavesi G (2007) Peripheral neuropathy in Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis. J Neurol Neurosurg Psychiatry 78:1119–1123
9. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, Maurier F, Jouneau S, Bienvenu B, Puéchal X, Aumaître O, Le Guenno G, Le Quellec A, Cevallos R, Fain O, Godeau B, Seror R, Dunogué B, Mahr A, Guilpain P, Cohen P, Aouba A, Mouthon L, Guillevin L, French Vasculitis Study Group (2013) Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 65:270–281
10. Seror R, Mahr A, Ramanoelina J, Pagnoux C, Cohen P, Guillevin L (2006) Central nervous system involvement in Wegener granulomatosis. Medicine (Baltimore) 85:54–65
11. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D (2007) Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 66:222–227
12. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15:539–553
13. Expert Panel on Detection (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285:2486–2497
14. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani RA (2009) Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 68:1827–1832
15. Suppiah R, Mukhtyar C, Flossmann O, Alberici F, Baslund B, Batra R, Brown D, Holle J, Hruskova Z, Jayne DR, Judge A, Little MA, Palmisano A, Stegeman C, Tesar V, Vaglio A, Westman K, Luqmani R (2011) A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis. Rheumatology (Oxford) 50:899–905
16. Shinohara Y, Tohgi H, Hirai S, Terashi A, Fukuuchi Y, Yamaguchi T, Okudera T (2007) Effect of the Ca antagonist nilvadipine on stroke occurrence or recurrence and extension of asymptomatic cerebral infarction in hypertensive patients with or without History of Stroke (PICA Study). Design and results at enrollment. Cerebrovasc Dis 24:202–209
17. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Roentgenol 149:351–356
18. Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 9:689–701
19. van Dijk EJ, Prins ND, Vermeer SE, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM (2005) C-reactive protein and cerebral small- vessel disease: the Rotterdam Scan Study. Circulation 112:900–905
20. Wada M, Nagasawa H, Kurita K, Koyama S, Arawaka S, Kawanami T, Tajima K, Daimon M, Kato T (2008) Cerebral small vessel disease and C-reactive protein: results of a cross-sectional study in community-based Japanese elderly. J Neurol Sci 264:43–49
21. Debette S, Markus HS (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 341:c3666
22. Arntz RM, van den Broek SM, van Uden IW, Ghafoorian M, Platel B, Rutten-Jacobs LC, Maaijwee NA, Schaapsmeerders P, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE (2016) Accelerated development of cerebral small vessel disease in young stroke patients. Neurology 87:1212–1219
23. Berden A, Göçeroglu A, Jayne D, Luqmani R, Rasmussen N, Bruijn JA, Bajema I (2012) Diagnosis and management of ANCA associated vasculitis. BMJ 344:e26
24. Pagnoux C, Guillevin L (2010) Churg-Strauss syndrome: evidence for disease subtypes? Curr Opin Rheumatol 22:21–28