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ORIGINAL COMMUNICATION

# Cerebral small vessel disease in patients with spontaneous cerebellar hemorrhage

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## Abstract

**Background** Spontaneous cerebellar-intracerebral hemorrhage (ICH) can be associated with both cerebral amyloid angiopathy (CAA) and hypertensive small vessel disease (HTN-SVD, i.e. arteriolosclerosis). To better understand the underlying microangiopathy of cerebellar-ICH, we aimed to evaluate the spatial distribution of supratentorial cerebral microbleeds (CMBs) and neuropathologic profiles in these patients.

**Methods** We enrolled consecutive cerebellar-ICH patients. Clinical variables and MRI markers specific for CAA and HTN-SVD were assessed. Patients were classified into categories according to the topography (strictly-lobar, strictly-deep, and mixed) of supratentorial CMBs and comparisons were performed. Available neuropathological material was reviewed to evaluate the presence and severity of arteriolosclerosis and CAA.

**Results** Ninety-eight cerebellar-ICH patients were enrolled. Fifty patients (51%) had at least one supratentorial CMB. Twelve patients (12%) had strictly lobar-CMBs, 12 patients (12%) showed strictly deep-CMBs and mixed-CMBs (lobar and deep CMBs) were present in 26 cerebellar-ICH patients (27%). In multivariable analysis, cerebellar-ICH patients with mixed-CMBs were associated with higher prevalence of hypertension (OR 4.9, 95% confidence interval [CI] 1.2–20, $p=0.017$) but with lower prevalence of severe centrum-semiovale enlarged perivascular spaces (OR 0.2, CI 0.05–0.8, $p=0.024$) when compared to cerebellar-ICH patients with strictly lobar-CMBs. Vascular risk factors and neuroimaging characteristics were similar between strictly deep-CMBs and mixed-CMBs. Six patients had available neuropathological material for analyses and they all showed some degree of arteriolosclerosis.

**Conclusions** Cerebellar-ICH patients frequently show supratentorial CMBs. The mixed-CMBs pattern appears to be the most common. Our radiological and pathological results suggest that the majority of cerebellar-ICH patients harbor HTN-SVD as dominant microangiopathy.

**Keywords** Cerebellar-ICH · Microbleeds · Small vessel disease

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## Introduction

The majority of spontaneous cerebellar intracerebral hemorrhage (cerebellar-ICH) is related to small vessel disease (SVD) [1, 2]. While some cerebellar-ICH appears to be associated with hypertensive small vessel disease (HTN-SVD; i.e. arteriolosclerosis), other cases show that cerebral amyloid angiopathy (CAA) may be involved [2, 3]. In clinical practice, it may be relevant to understand the underlying small vessel disease (SVD) type related to cerebellar-ICH, as CAA-related ICH are associated with higher risk of ICH recurrence than hypertensive ICH [4]. The location of the hematoma (i.e. lobar vs deep) and associated neuroimaging markers, such as cerebral microbleeds (CMBs), can help the clinicians to identify the dominant microangiopathy in supratentorial ICH [4]. However, in cerebellar-ICH the prevalent microangiopathy has not been precisely defined.

In this study, we aimed to assess the dominant SVD type (CAA vs HTN-SVD) in patients with cerebellar-ICH by evaluating the topographical distributions of supratentorial CMBs (defined as strictly-lobar, strictly-deep and mixed CMBs patterns) and available neuropathologic data.

## Methods

We performed a retrospective analysis of data drawn from an ongoing prospective cohort study of ICH performed at Massachusetts General Hospital (MGH; Boston, MA, USA) [2, 4, 5]. Study subjects were consecutive patients admitted to the MGH between January 1, 1998, and January 1, 2016, with spontaneous cerebellar intracerebral hemorrhage (ICH) [2, 5]. The term spontaneous cerebellar ICH is defined as a non-traumatic ICH in the cerebellar parenchyma, not secondarily caused by a tumour, vascular malformation, aneurysm or hemorrhagic transformation of ischemic stroke. Cerebellar-ICH occurring on oral anticoagulation were classified as spontaneous cerebellar-ICH. We included also patients who underwent a surgical evacuation. In all patients, secondary causes of cerebellar-ICH have been ruled out by means of CT angiography, MR angiography and MRI with gadolinium injections. Exclusion criteria were age $\leq 18$, primary intraventricular-ICH, supratentorial-ICH, brainstem-ICH and cerebellar-ICH patients who did not undergo an MRI during the hospitalization (Fig. 1).

This study was performed with approval and in accordance with the guidelines and ethical standard of the MGH

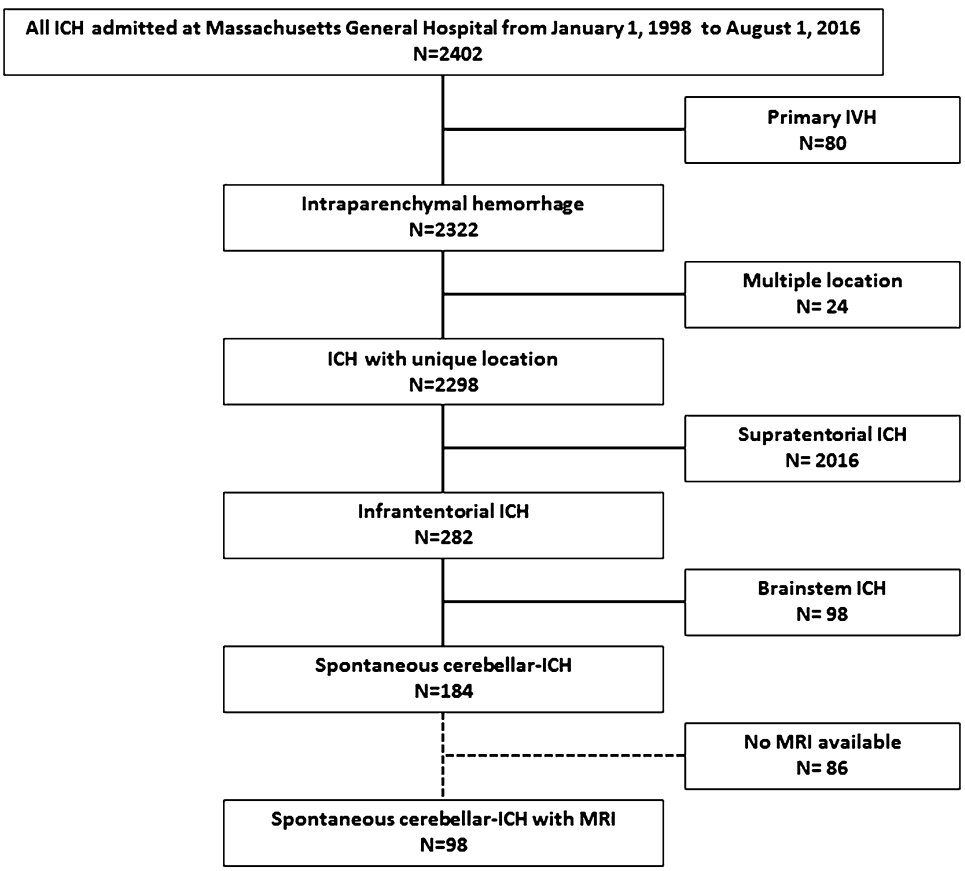


**Fig. 1** Flow chart of study enrollment

institutional review board, which allows us to collect data on all ICH patients treated at MGH.

## Baseline clinical data collection

As already described, hypertension was defined as previous diagnosis of hypertension or use of antihypertensive treatment for blood pressure control. Diabetes and hypercholesterolemia were defined as previous diagnoses or current use of antidiabetic and antihyperlipidemic drugs, respectively [2, 4]. History of previous ICH was also recorded.

## MRI data

Images were obtained using a 1.5 T MR scanner (GE Sigma) and included whole brain T2-weighted, T1 weighted, diffusion-weighted images (DWI), T2*-weighted gradient-recalled echo (T2*-GRE; echo time [TE] 750/50 ms, 5 mm slice thickness, 1 mm inter-slice gap) and fluid-attenuated inversion recovery (FLAIR; TR/TE 10000/140 ms, inversion time 2200 µs, 1 number of excitations, 5 mm slice thickness, 1 mm inter-slice gap). In seven cases, the blood-sensitive sequence used was Susceptibility Weighted Imaging (SWI). Neuroimaging markers of SVD severity were rated according to STRIVE consensus criteria [6]. CMBs were defined on axial blood-sensitive MRI as punctate foci of hypointensity less than 10 mm in diameter, distinct from vascular flow voids and leptomeningeal hemosiderosis. Their presence and number were evaluated according to current consensus criteria and categorized according to the previously validated Microbleed Anatomical Rating Scale [7, 8]. Patients were divided into three groups according to the location of supratentorial CMBs (strictly lobar-CMBs; strictly deep-CMBs; mixed-CMBs) [9]. Intrarater agreement for the presence of lobar, deep or mixed-CMBs was very good (Cohen $k = 0.84$). White matter hyperintensities (WMH) volume, presence of lacunes, presence of moderate to severe (defined as more than 20; [10]) basal ganglia (BG) and centrum semiovale (CSO) enlarged perivascular spaces (EPVS) and global brain atrophy were evaluated according to the STRIVE criteria [4, 6]. The presence or absence of cortical superficial siderosis (cSS) was evaluated in this study, according to current consensus criteria [11]. All MRI analyses were performed and recorded blinded to all clinical information.

To create a composite image of the spatial distribution of CMBs (Fig. 2) in cerebellar-ICH patients with strictly lobar-CMBs, strictly deep-CMBs and mixed-CMBs, the primary rater (MP) labeled each lesion using MRIcro. T1-weighted scans were co-registered to an intermediate target volume (one of the T1-weighted volumes that lacked any apparent structural defects) using affine registration (FLIRT, FSL). The target was then registered to an anatomical atlas (MNI305 volume). Manually marked lesions were subsequently resampled into the atlas space using the T1 coregistrations and 3D Slicer used to generate the composite figures. For displaying the position of lesions within the brain tissue, the brain was sub-divided into 10 mm 15 axial slabs and each lesion overlaid onto the middle slice of the slab [12].

## Neuropathology data collection

We reviewed and collected all available neuropathology information of primary cerebellar-ICH patients. Pathologic materials came from hematoma evacuation ($n = 26$), brain biopsy ($n = 1$) and full autopsy ($n = 1$). All specimens were processed using standard clinical pathology methods at our institution. Specimens underwent formalin fixation, standard paraffin embedding, hematoxylin-eosin staining, and immunohistochemistry directed against β-amyloid, or Congo red staining [13]. All slides were initially reviewed by diagnostic neuropathologists per clinical protocols. Twenty-two patients had only blood products from hematoma evacuation with no cerebellar parenchymal tissue or vessels available for examination.

All other available neuropathology slices containing cerebellar parenchymal tissue and blood vessels were also reviewed by 2 raters (MP and AC), blinded to clinical and MRI data. Following previous guidelines, we rated presence and severity of: (1) arteriolosclerosis: concentric hyaline thickening of small arteries, from 40 to 150 µm in diameter, leading to a stenosis of the vessel lumen [14], (2) presence or absence of vascular amyloid deposition confirmed by immunohistochemical detection or Congo red staining [15, 16]. Severity of the small vessel changes was rated using a semiquantitative scale ranging from 0 to 3 (0: normal, 1: mild changes, 2: moderate lesions, and 3: severe modifications) [14].

## Statistical analysis

Descriptive statistics were performed as frequencies for categorical variables as well as means and standard deviations for continuous variables. Demographics and clinical differences between cerebellar-ICH patients with and without MRI were explored in univariate analyses.

In cerebellar-ICH patients, 2 independent sample $t$ tests and Fisher's exact test were performed as appropriate to determine whether patients differed by pattern (e.g., strictly lobar-CMB vs strictly deep-CMB, mixed-CMB vs strictly lobar CMB, and mixed-CMB vs strictly deep CMB). Variables that were significant in univariate ($p < 0.05$) comparisons were entered in a logistic regression model. The only group comparison that had significant association for multivariate analysis was the comparison between strictly

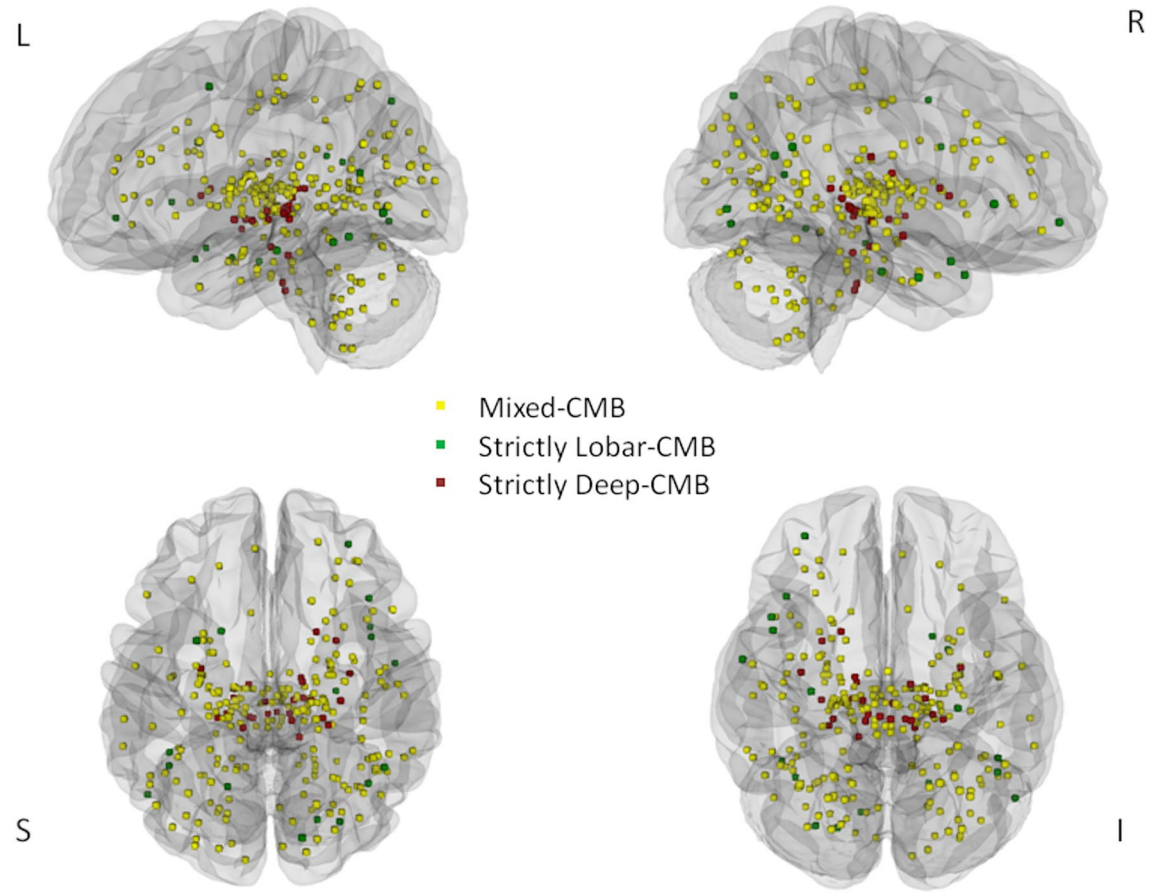


**Fig. 2** Topographical distributions of cerebral microbleeds (CMB) in cerebellar-ICH patients with strictly lobar-CMB, strictly deep-CMB and mixed-CMB

lobar-CMBs and mixed-CMBs. Presence of mixed-CMBs vs strictly-lobar CMBs was used as dependent variable. A $p$ value of $<0.05$ was considered statistically significant. All analyses were performed using JMP Pro 12 software (SAS Institute Inc).

## Results

Over a 18-year period, 184 spontaneous cerebellar-ICH were admitted to MGH. During hospitalization, 98 cerebellar-ICH patients underwent an MRI and were included in the study (Fig. 1). See Supplementary Table 1 for differences between cerebellar-ICH with and without MRI. Moderate to severe white matter hyperintensities (WMH) were present in 56%, lacunes were present in 43% and moderate/severe global brain atrophy was present in 35% of cerebellar-ICH patients (Table 1). Fifty patients (51%) showed at least one supratentorial CMB. In cerebellar-ICH patients with supratentorial CMBs, the majority showed a mixed-CMBs pattern ($n=26$). Twelve had strictly deep-CMBs and 12 patients had strictly lobar-CMBs. Figure 2 shows the distribution of strictly-lobar, strictly-deep and mixed-CMBs in this cohort of cerebellar-ICH patients. Thirteen patients (13%) of our cohort showed CMBs also in the cerebellum. Compared to the category with mixed-CMBs, strictly lobar-CMBs patients were older, with lower prevalence of hypertension but higher prevalence of more than 20 CSO EPVS (Table 1; all $p<0.05$). In multivariable analysis, history of hypertension was associated with the mixed-CMB category (OR 4.9, CI 1.2–20, $p=0.017$) while the presence of more than 20 CSO-EPVS with strictly lobar-CMBs (OR 0.2, CI 0.05–0.8, $p=0.024$). When compared to patients with strictly deep-CMBs, the mixed-CMBs group did not show any significant differences in demographic, clinical and neuroimaging variables. Finally, the strictly lobar-CMBs group had lower prevalence of history of hypertension but higher presence of more than 20 CSO-EPVS compared with patients with strictly deep-CMBs.

Out of 28 patients with pathological specimens only 6 patients had sufficient neuropathological materials for the evaluation of small vessel pathologies, which were used in this study. Supplementary table 2 reports the clinical, MRI and neuropathology finding of patients ($N=6$) in whom

**Table 1** Demographics, clinical and neuroimaging characteristics of all cerebellar-ICH patients and comparisons between patients with strictly lobar-CMBs, strictly deep-CMBs and mixed-CMBs

| Clinical and neuroimaging characteristics | Cerebellar-ICH $N=98$ | Strictly-lobar CMBs $N=12$ | Strictly-deep CMBs $N=12$ | Mixed-CMBs $N=26$ |
|---|---|---|---|---|
| Mean Age ± SD | 71.2 ± 13.2 | 77.2 ± 6.6 | 75.9 ± 11.6 | 74.3 ± 11.5* |
| Sex, female (%) | 47 (48) | 3 (25) | 7 (58) | 10 (38) |
| Hypertension (%) | 80 (81) | 7 (58) | 12 (100)§ | 25 (96)* |
| Diabetes (%) | 24 (24) | 3 (25) | 4 (33) | 6 (23) |
| Hypercholesterolemia (%) | 47 (48) | 7 (58) | 6 (50) | 9 (34) |
| History of ICH (%) | 6 (6) | 3 (25) | 1 (7) | 2 (8) |
| Atrial fibrillation (%) | 22 (22) | 4 (33) | 5 (42) | 8 (31) |
| Warfarin (%) | 23 (23) | 5 (42) | 4 (33) | 8 (31) |
| Antiplatelets (%) | 44 (45) | 5 (42) | 5 (42) | 16 (62) |
| Statins (%) | 34 (35) | 5 (42) | 2 (17) | 10 (39) |
| Moderate/severe WMH (%) | 55 (56) | 7 (58) | 8 (66) | 22 (84) |
| Presence of lacunes (%) | 43 (43) | 5 (42) | 7 (58) | 15 (58) |
| CSO-EPVS > 20 (%) | 11 (11) | 5 (42) | 0 (0)§ | 2 (8)* |
| BG-EPVS > 20 (%) | 30 (31) | 3 (25) | 3 (25) | 11 (42) |
| Any cSS (%) | 4 (4) | 1 (8) | 0 (0) | 3 (12) |
| Moderate/severe GBA (%) | 34 (35) | 4 (33) | 5 (42) | 14 (54) |

No significant differences ($p<0.05$) have been found in comparisons between mixed-CMBS and strictly deep-CMBS

*SD* standard deviation, *CMBS* cerebral microbleeds, *CVA* cerebrovascular accident, *ICH* intracerebral hemorrhage, *WMH* white matter hyperintensities, *EPVS* enlarged perivascular spaces, *CSO* centrum semiovale, *BG* basal ganglia, *cSS* cortical superficial siderosis, *GBA* global brain atrophy

*$P$ value < 0.05 in comparisons between mixed-CMBs and strictly lobar-CMBs

§$P$ value < 0.05 in comparisons between strictly lobar-CMBs and strictly deep-CMBs

these data were available. All 6 cases showed arteriolosclerosis on neuropathologic evaluation while CAA was absent in all the cases. Two mixed-CMBs patients showed moderate to severe arteriolosclerosis on pathology.

## Discussion

This study showed that supratentorial CMBs are commonly seen in patients with cerebellar-ICH. In our cohort, cerebellar ICH patients with supratentorial CMBs had predominantly a mixed distribution. Cerebellar-ICH with supratentorial mixed-CMBs appear more similar to cerebellar-ICH patients with strictly deep-CMBs than those with strictly lobar-CMBs. Evaluation of pathologic material showed that all cerebellar-ICH with pathologic data available had some degree of arteriolosclerosis. Overall, both our MRI-based data and neuropathologic results suggest that cerebellar-ICH patients appear to mainly harbor HTN-SVD as a dominant microangiopathy.

In line with older pathological series, our results suggest that the majority of cerebellar-ICH seems related to HTN-SVD and only a smaller proportion is associated to CAA [1, 3]. In our cohort, patients with supratentorial CMBs had predominantly a mixed distribution. Previous studies suggest that HTN-SVD may not only be located in deep areas but also involve lobar regions [4, 17]. Even if not confirmed by our limited pathologic data, cerebellar-ICH with strictly-lobar CMBs showed demographic, clinical and neuroimaging characteristics that may suggest presence of CAA pathology [4, 10].

Our study has limitations. Comparisons between different CMBs categories and neuropathologic evaluation was limited by sample size despite being the largest consecutive series of cerebellar-ICH patients with a detailed MRI assessment to date. To answer to our research question, we decided to use two different methodological approaches, such as MRI and neuropathology. Each of these technique provide different degrees of evidence for the diagnosis of the underlying SVD pathology in cerebellar ICH patients. Furthermore, patients with enough pathological materials for analyses were much less compared with the whole samples with MRI. These two aspects might have created a certain degree of inhomogeneity for the different weights the two methodological approaches brought to the results. However, as gold standard for diagnosis in medicine, the use of pathologic evidences enabled us to support our MRI results showing that in cerebellar-ICH arteriolosclerosis might be present.

We, also, acknowledge that almost half of cerebellar-ICH patients did not show supratentorial CMBs on MRI. Therefore, the systematic evaluation of supratentorial CMBs in cerebellar ICH remains matter of debate in clinical practice.

Finally, cerebellar ICH patients that did not undergo an MRI were associated with larger hematoma volume compared to included patients. This might have created a selection bias because we cannot exclude that cerebellar ICH patients with larger volumes harbor a different ICH etiology. Overall our results must, therefore, be considered hypothesis generating and exploratory.

In conclusion, both our MRI and pathological results suggest that cerebellar ICH patients appear to mainly harbor HTN-SVD, as a dominant microangiopathy. Further studies in larger cohorts with pathologic evaluation are required.

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## Compliance with ethical standards

**Conflicts of interest** All authors declare that they have no conflict of interest.

## References

1. Dinsdale HB (1964) Spontaneous hemorrhage in the posterior fossa: a study of primary cerebellar and pontine hemorrhages with observations on their pathogenesis. Arch Neurol 10:200–217
2. Pasi M, Marini S, Morotti A et al (2018) Cerebellar hematoma location: implications for the underlying microangiopathy. Stroke 49:207–210
3. Itoh Y, Yamada M, Hayakawa M et al (1993) Cerebral amyloid angiopathy: a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. J Neurol Sci 116:135–141
4. Pasi M, Charidimou A, Boulouis G et al (2018) Mixed-location cerebral hemorrhage/microbleeds: underlying microangiopathy and recurrence risk. Neurology 90:e119–e126
5. Falcone GJ, Brouwers HB, Biffi A et al (2014) Warfarin and statins are associated with hematoma volume in primary infratentorial intracerebral hemorrhage. Neurocrit Care 21:192–199
6. Wardlaw JM, Smith EE, Biessels GJ et al (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12:822–838
7. Greenberg SM, Vernooij MW, Cordonnier C et al (2009) Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 8:165–174
8. Gregoire SM, Chaudhary UJ, Brown MM et al (2009) The Microbleed Anatomical Rating Scale (MARS) reliability of a tool to map brain microbleeds. Neurology 73:1759–1766
9. Caunca MR, Brutto VD, Gardener H et al (2016) cerebral microbleeds, vascular risk factors, and magnetic resonance imaging markers: the Northern Manhattan Study. J Am Heart Assoc 5:e003477
10. Charidimou A, Boulouis G, Pasi M et al (2017) MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. Neurology 88:1157–1164
11. Charidimou A, Linn J, Vernooij MW et al (2015) Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. Brain 138:2126–2139
12. Auriel E, Gurol ME, Ayres A et al (2012) Characteristic distributions of intracerebral hemorrhage—associated diffusion-weighted lesions. Neurology 79:2335–2341
13. Charidimou A, Martinez-Ramirez S, Shoamanesh A et al (2015) Cerebral amyloid angiopathy with and without hemorrhage evidence for different disease phenotypes. Neurology 84:1206–1212
14. Deramecourt V, Slade JY, Oakley AE et al (2012) Staging and natural history of cerebrovascular pathology in dementia. Neurology 78:1043–1050
15. Vonsattel JPG, Myers RH, Tessa Hedley-Whyte E et al (1991) Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann Neurol 30:637–649
16. Greenberg SM, Vonsattel J-PG (1997) Diagnosis of cerebral amyloid angiopathy: sensitivity and specificity of cortical biopsy. Stroke 28:1418–1422
17. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD (2003) Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 62:1287–1301